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Eosinophilic Esophagitis: A Comprehensive Review

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Abstract

Eosinophilic Esophagitis (EoE) has been the subject of intense research and study over the past few years, as incidence and prevalence has increased in the United States, especially in adults. The signs, symptoms and complications of EoE arise from a complex interplay of genetic predisposition and environmental exposure that is not understood well at this time. The disease causes significant morbidity in both physical and psychological areas, and these effects may become permanent in some cases where remodeling of the epithelium is present. Treatment at this time mainly focuses on diet, medication and endoscopic dilation. While none of these entities can accomplish all of the treatment goals, careful selection of patients based on symptoms and physical findings can alleviate many of the complications of the disease. In addition, this review attempts to cull data from adult studies if possible, as much of the studies that involved children did not translate well to adult patients.

Keywords: Eosinophilic esophagitis; Fibrostenotic disease; Esophageal dilation

Introduction

The topic of eosinophilic esophagitis (EoE) has been the subject of intense study and controversy over the few past years. Shelved as an "orphan disease" rarely seen outside the world of pediatrics, EoE has seen a steady increase in incidence in adults and children over the years, and has shown to be a very difficult disease to diagnose properly and treat effectively. This article attempts to bring together the relevant data regarding the complicated epidemiology, pathophysiology of the disease and offer assistance in diagnostic and therapeutic strategies. Specifically, this review attempts to cull data from adult studies if possible, as much of the studies that involved children did not translate well to adult patients. This has much to do with the natural history of the disease, as we will find out later.

Epidemiology

Eosinophilic esophagitis was first described in 1978 by Landres [1] and in 1982 Munch [2] although Attwood et al. were the first to propose this as a distinct clinical entity in a case series of 12 patients [3]. Interestingly, all of these initial patients described were adult patients. A review of the literature as time progresses shows an abundance of pediatric cases compared to adult ones. In his editorial, Gawron et al. postulates that this was likely due to pediatric gastroenterologist taking routine biopsies of the esophagus [4]. For many years after, EoE was thought to be a disease seen predominately in children.

New data, however, shows that adults have at least as much risk as children for EoE. A study by Dellon et al. looking at ICD-9 codes showed a prevalence of 58.9/100,000 in persons greater than 20 years of age vs. 50.5/100,000 in those less than 20 years of age, with peak prevalence in the 35-39 age range [5]. Another single center study looking at 1357 adult VA patients referred for elective endoscopy showed 1.8% of those patients had probable or definitive EoE [6]. Other studies postulate that this number might be even larger still, as patients may have been missed as a result of under recognition due to the rigors of histologic and endoscopic criteria for diagnosis [7].

The most vexing question is whether patients were under-diagnosed in the past, or has the incidence of the disease risen over recent years. If we look at just histology, there is evidence that the rate of esophageal eosinophilia has not increased over the past 15 years. In a retrospective study looking at consecutive esophageal mucosal biopsies from May-June in 1990 and 2005, no difference was seen in the prevalence of esophageal eosinophilia, defined as >20 eosinophils/hpf in this study [8]. However, clinical evidence of increasing incidence of EoE in adults has been noted since at least 2005 [9]. Studies in adult in Olmsted County Minnesota and Switzerland have appeared to confirm this increase as well [10,11].

It is unlikely that the disease would be as underdiagnosed as the histology data purports. As Bonus and Furuta astutely point out in their review article, the technique of barium esophagram has been available for several decades and is usually included in the workup for dysphagia, however, no mention of large amounts of "ringed esophagus" patient populations are mentioned in the literature [12]. In fact, the radiographic evidence of EoE was rare enough in the past that it was reported in several case studies as a subset of reflux disease [13,14].

The theory that the increase in incidence is due to increases in esophageal biopsies is a controversial one. A Canadian study from 2004-2008 supports this, however a more recent Danish study demonstrates a minimal effect if any [15,16].

One way to assimilate this data is to note that the presence of eosinophilia in the esophagus does not automatically point to a diagnosis of EoE. As we will discuss later, there are many causes of eosinophilia in the esophagus (reflux, inflammatory bowel disease etc.), and these other causes may account for the majority of eosinophilia in the esophagus in past years [16].

One theory that could explain the discrepancy could be that the rise in EoE may have been countered by a decrease in another cause of eosinophilia, such as GERD related disease. The theory has some merit, as the effective use of proton pump inhibitors has become ubiquitous in the treatment of heartburn. In this way, the rise in EoE is accounted for while preserving the overall rate of eosinophilia (Figure 1).

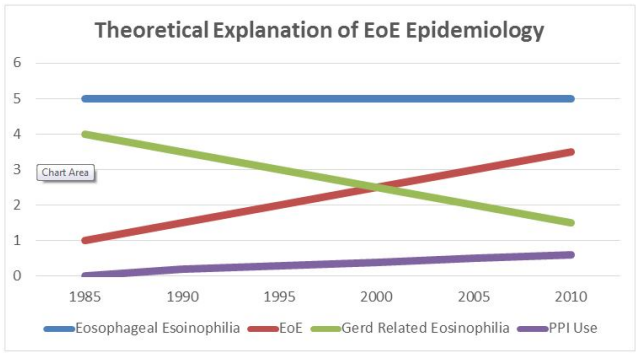

Figure 1: Theoretical explanation of EoE epidemiology.

Differences in Clinical Presentation between Adults and Children

EoE presents similarly in children and adults with respect to demographic data, with a male predominance of 3:1 and increased prevalence in Caucasians. However, there are clear differences in the clinical presentation of adults and children. Adults tend to present with dysphagia (70-80%) and food impaction (33-54%) whereas children commonly present with reflux, vomiting and abdominal pain [17]. A Preliminary Study of 74 Adults and 101 Children showed the striking difference between these age groups (Table 1) [18].

	Adult	Child
Number of Patients	74	101
Age (average in years)	38+/-12	5.5+/-2
Male (ratio)	0.125694444	0.125694444
Duration of Symptoms (years)	6.9+/-3	1.2+/-1.5
Allergy History (%)	88	84
Presenting Symptoms (%)		
Dysphagia	92	7
Food Impaction	58	9
Heartburn	27	2
Abdominal Pain	7	33
Nausea Vomiting	4	69
Growth Failure	0	31

Table 1: Similarities and differences in adult and child presentation in EoE.

Later, an expanded analysis of this group showed the differences extended to endoscopic findings as well. Adults tended to present with concentric rings (82%) and linear furrows (70%), with very little white plaques (14%) or normal esophagus (1%). In contrast the most common findings in children were linear furrows (39%) white plaques (35%) and normal esophagus (30%), with only 3% presenting with rings. Further analysis showed that rings were only seen in older children and white plaques were only seen in young adults. This re-enforces the theory that children present differently and have different endoscopic findings from adults because they may be expressing the disease at different points in the disease course (Table 2) [19].

	Adult	Child
Number of Patients	200	120
Age (average in years)	39	4.7
Male (%)	75-76	75-76
Duration of Symptoms (years)	8.3+/- 6	1.2+/-1.5
Peripheral Eosinophilia (%)	11	73
Endoscopic Findings (%)		
Concentric Rings	82	3
Linear Furrows	70	39
White Plaques	14	35
Normal	1	30

Table 2: Endoscopic findings in adults and children with EoE.

Adults tend to have a larger delay in diagnosis and therefore have issues with fibrostenotic disease while children are diagnosed earlier when inflammatory disease drives their symptoms. This difference in pathophysiologic presentation not only affects presentation, but extends to treatment options and response to treatment as well [20]. A recent multicenter trial by Singal et al. appears to corroborate this data with adults, with younger patients that had a shorter course of symptoms having more inflammatory disease than fibrostenotic disease than older patients who have endured symptoms longer [21].

It is important to note that it may be difficult to ascertain the breadth and severity of symptoms in patients with EoE, as many patient, especially adults, have developed coping mechanisms, such as cutting food into little pieces, avoiding certain foods altogether and drinking an abundance of liquids with food [22].

Pathophysiology

Eosinophils are normally not seen in the esophagus. They are recruited there through Th2 and IgE mediated pathways, similar to those seen in food allergies, gastrointestinal reflux disease, and inflammatory bowel disease. The process and pathways are incompletely understood, but there appears to be complex interplay between acid exposure, environmental and food allergens, and genetic factors that predispose patients to the disease.

Acid exposure

The role of acid exposure in the esophagus in EoE is complex and poorly understood. As Gonsalves has pointed out, in the past it was

incorrectly thought that higher levels of eosinophilia in the esophagus were related to EoE, while lower levels pointed to reflux disease [19]. A study of 35 adults with esophageal eosinophila has shown that PPI administration is effective in reducing eosinophil counts, including a 50% response rate in patients with "EoE phenotype" and 33% of patients with negative pH studies [23].

The possibility that acid exposure of the epithelial cells might increase permeability to potential allergens is still posited as a mechanism, and this may lead to further activation of the inflammatory cascade [24].

Environmental and food allergens

The immune mediated response in EoE has been compared to the allergic response seen in other conditions. The allergic response model appears to be validated in animal studies, where it was found that T cell-deficient, but not B cell-deficient, mice appear unable to develop EoE [25]. Not surprisingly, epidemiological data in adults shows that the prevalence of atopy (70-80%) asthma (12-38%) and allergic rhinitis (17-70%) in EoE patient is higher than the general population [17]. A recent study conducted by an otolaryngology groups found that patients with chronic rhinosinusitis had a 3.4 fold increase in having EoE [26].

Previous studies had thought that adult disease was driven by aero-allergens while childhood disease was primarily from food allergies [22]. More recent studies by Gonsalves et al. and Lucendo et al. have now made it clear that food allergies are significantly involved in the development of EoE in both children and adults [27,28]. There are some differences in the types of food that trigger symptoms between adults and children, with adults are more likely to be susceptible to tree nuts [19].

Aeroallergens, though, could also play a minor role in triggering the disease as well. Studies have shown that most adults (and children) are sensitized to aeroallergens [29], and that the incidence of EoE diagnosis has a seasonal variance, with the lowest point in the wintertime [11].

In a mouse study, it was shown that epicutaneous presentation of an antigen was found to "prime" the immune system and result in esophageal eosinophilia when exposed to a single airway antigen challenge [30].

However, care must be made in interpreting reactivity to these allergens, especially through skin testing, as there is low correlation between these tests and actual triggers [19]. In addition, there are instances where no IgE mediated allergens can be found though IgE or skin prick testing [20].

Regardless of the source, reduction of allergen exposure and allergic triggers have been shown to be an effective method in reducing the effects of the disease.

Other environmental exposures–oral tolerance

There are other non-allergen entities which appear to have some effect in inducing the EoE phenotype. Early antibiotic use in infancy may predispose patients to the disease as well as caesarean delivery [20,31,32]. There has also been shown to be an inverse relation with EoE and h pylori infection, with a case sample size of over 5000 adult and pediatric patients showing an odds ratio of 0.79 of EOE among infected individuals [33].

As Jensen and Dellon point out in their review article the common link between these components may be that these entities may interfere with oral and immune tolerance, the process by which the human body interacts with the millions of potentially antigenic particles in the environment [34]. A recent study showing the esophageal microbiome in EoE patient to be different than that of controls may further this notion [35].

Genetics

When taking a careful history, many patients have a family history of atopy or EoE [36]. This suggests that there may be genetic defects that may predispose patients to develop the disease. *In vitro* studies have shown esophageal epithelial cells of EoE patients have mutations in an epidermal differentiation complex gene called filaggrin, which binds to keratin fibers in epithelial cells and is important in barrier integrity in these cells [37]. Other studies in children have found genomic defects in the 5q22 chromosome, specifically those that code for thymic stromal lymphoprotein, which is involved in Th2 mediated cytokine response pathways [38].

In early studies using genome wide microarray analysis, patients with esophageal eosinophilia showed a "striking transcript signature" in the gene that encodes the chemoattractant eotaxin 3 (CCL26) that was "conserved across sex, age, and allergic status and was distinct from that associated with non-EE chronic esophagitis" [39]. This has led to an "EoE diagnostic panel", a genomic test available at academic centers, which has been shown in small randomized controlled trial to have a sensitivity of 96% and a sensitivity of 98% with respect to the diagnosis of EoE [40].

Later studies involving genomic wide associations studies (GWAS) have reported associations with variants at the c11orf30 locus (polysensitization of allegen) [41], STAT6 gene (allergic sensitization and serum IgE) [42], and CAPN14 (calcium regulated protease that is highly expressed in esophageal mucosa and is associated with filaggrin) [43]. Future studies will lead to more information of the role of genetics in this complicated interplay of genes and environment.

Immune–mediated response

The cascade of the Th2 mediated pathways that are stimulated by triggers in these genetically predisposed individuals is complex and slowly being understood, and generally beyond the scope of this review article. What we can say on a very basic level is that there are two major types of pathways.

A "local" reaction whereby epithelial cells are stimulated to express TNF-α and eotaxin-3 directly, which are known to recruit eosinophils to the esophagus. Thymic stromal lymphopoeitin (TSLP) has also been known be released from epithelial cells, which has direct effects on Basophils and Eosinophils and also has cytokine effects favoring Th2 differentiation.

A "systemic" effect whereby TSLP promotes a dendritic (antigen presenting)
cell–mediated cell Th2 response, which activate cytokines such as IL-4, IL-5, IL-9, and IL-13. These intermediaries activate mast cells and eosinophils, and cause B cells to release antibodies including IgE, which can further activate mast cells and basophils (Figure 2) [30].

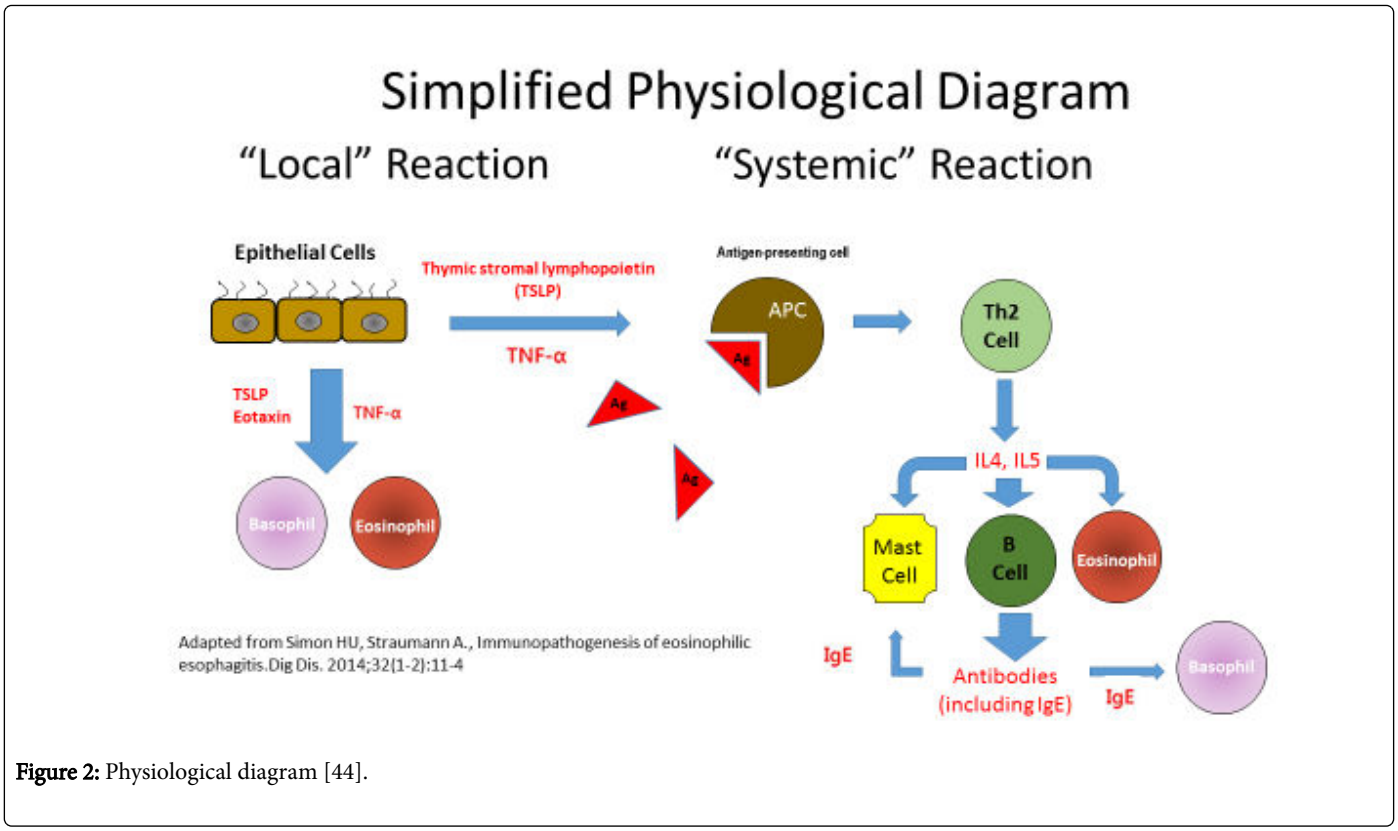

Figure 2: Physiological diagram [44].

The end result is the release of eosinophil and mast cell products, which stimulate and regulate the inflammation and remodeling of the esophagus through profibrotic and proangiogentic factors, such as Major Basic Protein (MBP), Transforming Growth Factor Beta 1 (TGF-β1) and other entities (Chemokine ligand 18 (CCL-18), Vascular endothelial growth factor (VEGF) vascular cell adhesion molecule 1 (VCAM-1)).

Major Basic Protein has been shown in studies to increase Fibroblast Growth Factor-9 levels and epithelial cell proliferation, leading to basal cell hyperplasia, one of the hallmark histological signs of both EoE and GERD.

Transforming Growth Factor Beta 1 has been shown in *in vitro* studies to upregulate expression of epithelial mesenchymal transition (EMT) genes, such as N-Cadherin, vimentin and Fibronectin [45].

TGF-β1 also has been shown to have angiogenic properties which may serve to increase tissue damage by increasing recruitment of inflammatory cells [46].

In this way, TGF-β1, along with IL-13 and IL-4, serve to activate and regulate many of the end organ sequalae of EoE through fibroblast activation and myofibroblast trans differentiation and production of extracellular matrix proteins (collagen, tenascin-C).

These processes lead to sub epithelial fibrosis and alternation in smooth muscle contraction, which in result in the rings and strictures seen on endoscopy and the dysphagia experienced by patients [47].

Diagnosis

The diagnosis of EoE is difficult at times, as it is not based exclusively on the histology of esophageal eosinophilia.

There are many conditions that may involve increased eosinophils in the esophagus (Table 3) [48].

Diseases associated with esophageal eosinophilia
Eosinophilic gastrointestinal diseases
PPI*-responsive esophageal eosinophilia
Celiac disease
Crohn's disease
Infection
Hyper-eosinophilic syndrome
Achalasia
Drug hypersensitivity
Vasculitis
Pemphigus
Connective tissue diseases
Graft vs. host disease
*PPI = Proton-pump inhibitor

Table 3: Diseases associated with Eosinophilic Esophagitis.

The diagnosis of EoE should be made on the basis of clinical symptoms and endoscopic, histological, and radiographic findings. This table attempts to compile these findings from studies using large cohorts of patients (Table 4).

Symptoms	% [17,49,50]	Endoscopy	% [19,51]	Histology [51]	Other Findings	% [19]
Dysphagia	70-80	Circular rings (feline esophagus)	82	Eosinophilia (>15 eos/hpf)	Peripheral Eosinophilia	11
Food Impaction	33-54	Strictures (upper)	11628	Eosinophilic micro abscesses		
Heartburn	30-60	Attenuation of the vascular pattern	41	Sub epithelial and lamina propria fibrosis and inflammation		
Chest Pain	16285	Linear Furrows	70	Basal Cell Hyperplasia		
Atopic Diseases	20-80	Whitish Papules/Plaques	14	Papillary Lengthening		
		Small Caliber Esophagus	10	Increased number of mast cells, B cells		
		Normal Esophagus	1			

Table 4: Typical symptoms and findings seen in adult Eosinophilic Esophagitis.

Though endoscopy is certainly a required component in the diagnostic workup of EoE, endoscopic findings are not well correlated to the presence or severity of disease. Early meta-analysis of 100 studies showed poor sensitivity (15-48%) and high specificity (90-95%) of these findings [52]. A new validated scoring system, the EoE Endoscopic Reference Score (EREFS), has been tested and validated across expert and non-expert endoscopists, which should help standardize these features across all EoE patients [53].

It is important to note that different diagnostic tests might be helpful in distinguishing different phenotypes of EoE. For example, a recent study of 58 patients at the Mayo Clinic has shown that barium esophagram is the most accurate method to determine the diameter of the esophagus, and thus patient more susceptible to dysphagia symptoms [54]. In addition esophageal manometry studies may help in identifying motility issues relating to the remodeling of the esophagus, as evidenced by a pan esophageal pressurization similar to achalasia that is seen in up to 50% of EoE patients [55].

Proton pump inhibitor responsive Esophageal Eosinophilia

Particularly hard to distinguish from EoE is Proton pump inhibitor responsive esophageal eosinophilia (PPI-REE). In fact, according to the ACG guidelines, it is unclear if PPI-REE is a subset of EoE, a consequence of GERD, or a clinical entity all its own [48]. It has been shown through a meta-analysis of 10 trials of 258 patients (152 children and 106 adults) is that at least 1/3 of patients with suspected EoE on histology will benefit clinically and histologically from a proton pump inhibitor [56]. This was further re-enforced by a randomized control trial by Moawad et al. of 42 patients with Esophageal Eosinophilia that were randomized to fluticasone 440 mcg BID vs esomeprazole 40 mg qd. There was no significant difference in resolution of esophageal eosinophilia (<7 eosin/hpf) between groups. The authors further analyzed the data, which included 24 hour ph and impedance testing of each arm. It turned out that none of the patients (0/4) with documented reflux via Johnson-Demeester score had histologic resolution with topical glucocorticoids while all of the patients (4/4) with reflux benefitted histologically from a PPI [57]. Efforts to further distinguish EoE from PPI-REE have proven difficult. Endoscopic and clinical characteristics appear to be similar [58]. Earlier studies by Francis et al. have shown that even ambulatory pH monitoring is not reliable in predicting response to PPI [59]. Unfortunately, to further complicate the issue, there was a small subset of 4 children who initially responded to PPI, but developed signs and symptoms of EoE as time progressed. At this time it is unclear if this is a separate pediatric sub-phenotype or a manifestation of all PPI-REE [60]. Based on the available data then, the ACG guidelines recommend that patients suspected of EoE undergo a trial of PPI for 2 months, at which time an EGD is performed and the esophagus is re-biopsied. There is no data on which dose to use, although most trials use twice a day usage [48]. Obviously there may be insurance and compliance issues regarding the procurement and administration of the medications. A recent poster presentation at UEGW has shown that patients with PPI-REE can have long term histological response when treated with a PPI, even when the dose of PPI was lowered in a majority of patients [61]. In lieu of the ever increasing risks of long term PPI therapy, this treatment strategy should be carefully considered.

Histologic diagnosis

The number of biopsies is crucial to establish the diagnosis of EoE. Current guidelines have somewhat arbitrarily defined this as a single esophageal biopsy showing 15 eosinophils/hpf. ACG guidelines recommend that "2-4 biopsies be obtained from two areas of the esophagus" as there may be sample error [48]. Recent studies have shown more biopsies result in a higher chance of diagnosis. A study by Nielsen et al. of 102 sequential cases of Confirmed EoE with Mid And Distal Esophagus biopsies showed that 4 biopsies resulted in 98% probability of detecting >15 eosinophils/hpf. The study also advises that biopsies be taken in the proximal esophagus to distinguish from reflux esophagitis [62]. Newer histological scoring systems that take into account other inflammatory characteristics, such as eosinophil density, epithelial markers of inflammation such as dilated intracellular spaces, and fibrosis of the lamina propria may soon make diagnosis easier and treatment response more accurate [63]. One possibility that would explain why multiple biopsies are needed to reliably diagnose EoE may lie with the fact that eosinophils in EoE may not be able to be seen on H and E stains. Results of Electron Microscopy Show that greater than 98% of Eosinophils in EoE demonstrated morphological abnormalities, including granule staining reversal, loss of cellular

membrane, and marked cytoplasmic vesiculations [64]. Questions arise as to whether biopsies of the stomach and duodenum should be routinely taken in adults with EoE. The ACG guidelines state that biopsies should only be taken if there are clinical or endoscopic findings that warrant taking biopsies, although more studies are likely needed with respect to adult disease [48]. This is somewhat controversial as the disease course of eosinophilic gastritis and duodenitis have different disease course and different treatment regimens.

Why treat the disease?

Patients should consider treatment as soon as they are definitively diagnosed. Unlike children, adult patients are usually diagnosed many years after symptoms begin, with one Swiss study showing a mean delay in diagnosis of 6 years [65]. Studies have also shown that a great majority (86%) of patients will have fibrosis and remodeling of the lamina propria over the course of the disease [66]. In addition there appears to be a linear progression of the disease with respect to fibrosis. In one study the odds ratio for fibrosis more than doubled for every 10 years of disease [67], and that stricture prevalence increased with greater delays in diagnosis [61]. Most ominously, as the disease progresses in adulthood, there may be difficulties in reducing and reversing these remodeling changes [45]. Although measuring the quality of life impact of EoE is difficult and still being formulated, early studies in children suggest that the disease affects not only gastrointestinal issues, but result in social difficulties, anxiety, sleep difficulties, and depression, with an increasing incidence as these children age [68]. Clearly the designation of EoE in some textbooks as a benign, slowly progressing disease minimize the impact of the disease on patients and the need for prompt treatment in many cases.

Treatment strategies

Treatment strategies involve several different targets along the immune modulation pathway, including reducing offending allergens, reducing the immune-mediated response and tissue effects with medication, and dilation of strictures and fibrosis. Goals of therapy should include alleviation of symptoms, improving quality of life and limiting disease progression which can lead to complications. At times, multiple strategies are pursued at the same time. The treatments generally fall into 3 categories: Dietary Restriction, Medical Therapy including glucocorticoids and acid suppression therapy, and Esophageal Dilation (Figure 3) [69].

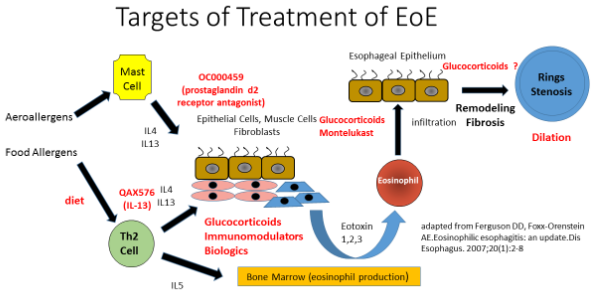

Figure 3: Targets of treatments in Eosinophilic Esophagitis.

Dietary restrictions

There are three strategies regarding dietary restriction in EoE patients: An elemental diet, which patients consume free amino acids, medium chain triglycerides, and corn syrup solids only using allergy testing, namely skin prick testing (SPT) and atopy patch testing (APT) to find offending foods and eliminate them from the diet and empiric elimination of the most common foods that cause hypersensitivity (Milk, eggs, soy, wheat, peanuts/tree nuts, fish/shellfish), foods are then re-introduced over time.

Elemental diet

Elemental diet therapy has shown by far to be the most effective option in children. 4 pediatric trials ranging from 10-172 patients showed a symptomatic effectiveness in 96-100% [70-73]. Likewise, a recent meta-analysis of 429 patients heavily skewed toward children showed 90% effectiveness in histological improvement [74].

Unfortunately, there is much less data for adults, and the data that is available is not as encouraging. A great example of this is the study by the Peterson Group in Salt Lake City, Utah, which looked at a 2 to 4 week trial of an elimination diet in adults. Of 29 adults (56% male) that started the trial, 11 were not able to tolerate the diet and dropped out of the study. Of the 18 patients left, 72% of patients had a complete or near complete histological response (<10 eosinophils/hpf). Mast cell content, parabasal layer thickness, and endoscopic furrows and exudates also significantly decreased. Unfortunately, though, symptoms and esophageal strictures were not improved. Several patients also experienced significant weight loss on the diet as well [75]. As pointed out by the author in a later review article, the poor effectiveness may have been a result of selection bias, as likely only severely affected patients enrolled in the trial [76]. The difficulty in compliance is not unique to this adult trial; looking back at earlier studies with children, we can the incredible difficulties in maintaining this diet. In a study by Markowitz et al in 2003, only 3 of 51 children were able to tolerate the diet orally, the rest required nourishment via naso-gastric tube [68]. This combined with potential costs, insurance issues and inconveniences associated with purchasing the supplements make an elemental diet choice an option in only a select few patients.

Skin testing directed diet restriction

Using allergy testing to detect food allergies and eliminating these foods in the diet appears to be a sensible and scientific method of dietary restriction. Earlier studies by Spergel et al. in children were very encouraging, with 92% symptomatic improvement and 77% histologic improvement rates seen. However, these exceptional data were not able to be repeated in later studies, in which effectiveness hovers in the 40-53% range [77-79]. Again, data in adults is scarce, and analysis of efficacy is not encouraging. In a trial with 15 adults, Molina-Infante et al. found only 4/15 patients showed complete response, and 1/15 with partial response after SPT, APT and PPT testing [80]. Another study showed only 1/6 EoE patients who were determined to be sensitized to wheat and rye on SPT test responded to a directed diet, and that patient only responded symptomatically [81].

The difficulties with allergy directed diets stem from the fact that the treatment is based on the premise that EoE is based primarily on IgE mediated pathways. As multiple studies have shown, the EoE response is complex and involves cell-mediated as well as IgE components. This manifests itself in the fact that food-specific IgE serum measurements and SPTs are neither sensitive nor specific methods for predicting EoE

triggers in adult patients [27,28,82]. Skin Prick Testing and Atopy Patch Testing are also notoriously unreliable. After reviewing multiple studies looking at the accuracy of these studies, Wechsler et al. remarked in his review article that "while negative tests are somewhat encouraging (except for milk), positive tests often lead to a false positive result" [79].

While this high false positive rate may seem trivial at first glance, a look at a study of 146 children showed that 40 were placed on elemental diet based on SPT and APT testing alone [74]. The significant morbidity, logistics and expense of placing patients on an elemental diet have been documented earlier. In addition, skin testing directed diet restriction may be particularly fruitless in adults as opposed to children. In a paper by Lucendo et al., it is postulated that differences in anatomic and physiologic characteristics of the gastrointestinal systems of adults and children may contribute to the disparities in results.

Younger patients have less integrity to the barrier of their gastrointestinal tract, and have an immature enzymatic system, which results in absorption and presentation of partially digested dietary peptides which mediate IgE through Th2 mediated pathways. As the integrity of the barriers improve and enzymes cleave the peptides, the IgE hypersensitivity response is diminished, and skin testing loses its value [83,84].

Foods Removed in SFED Diet	
Milk	Eggs
Soy	Wheat
Peanuts/Tree Nuts	Fish/Shellfish

Table 5: Typical foods removed initially in SFED diet.

Empiric elimination diet

The Six Food Elimination Diet (Table 5), or SFED diet also had promising data in earlier trials with children [71,85,86]. The difference is that these studies translated well to adults. In a prospective study of 50 adult patients with EoE studied for 6 weeks on the SFED diet, 94% had symptomatic improvement, 64% had complete histologic response and 70% had complete or near complete response. As a side note, prospective SPT testing in these patients did not predict a response to diet [27].

In addition, another prospective trial of 67 patients treated with SFED (plus rice, legumes, and corn) for 6 weeks showed that 73% had histological remission after diet, and that remission continued up to 3 years if the diet was continued. Again IgE and/or SPT measurements were not predictive of food allergy.

What is interesting about this study as well was that the additional food elimination was tailored to local food allergies (the study took place in Spain) [28]. SFED diets have also proven to be more effective than allergy testing directed therapy in a small retrospective cohort of 31 patients at UNC-Chapel Hill. SFED showed greater symptom improvement rate (78% vs. 68%) histological response rate (75% vs. 50%) and histological remission rate (56% vs. 32%) [87]. This data was also supported in a meta-analysis, by Arias, in which SFED (72.1%) was significantly better than Targeted Diet (45.5%). In Reducing Histology of Eosinophillic Esophagitis to <15 eosinophils/hpf [71].

The problems and possible danger of this treatment occur when trying to re-institute foods into the diet. Typically diets are followed for 6-8 weeks, and then repeat biopsies of the esophagus are performed. If there is histological remission, foods are then re-introduced one at a time and repeat biopsies are taken after a similar period of time. Besides the expense, risk and inconvenience of repeat endoscopies with biopsies, results can be confounded by non–compliance with diet or possibly even aero-allergens [25].

In addition there is a theoretical danger that re-introduction of foods can cause IgE sensitization. Studies have shown that loss of tolerance of foods such as milk or nuts can occur when food is removed [87]. Therefore, patients with significant food specific IgE serum levels or positive skin prick testing should, according to the guidelines from Journal of Allergy and Clinical Immunology in 2011, be supplied with an injectable epinephrine to guard against anaphylaxis [17].

In the future there may be new, less invasive techniques which can make food re-introduction easier from a logistical and invasive standard. One of these techniques could be tethered confocal endomicroscopy capsule, which is being tested in *ex vivo* and *in vivo* in animals and shows some promise [88].

Serum IgE-targeted elimination diet

There was a study in 2014 by Rodriguez-Sanchez et al., that was the first comparative prospective study of a serum IgE-targeted elimination diet vs. SFED diet in a small group of adults that showed a better histological response to serum IgE directed therapy (73%) than SFED diet (53%), although the difference was not statistically significant and the study suffered from significant selection bias [89].

Medical Therapy

Topical glucocorticoids

The use of topical glucocorticoids has been used extensively in the treatment of EoE. Typically there are three methods of administration. The first involves swallowing the contents of an inhaler typically used by asthmatics, containing fluticasone propionate or ciclesonide. A spacer is not used and the medication is swallowed. Other methods involving budesonide require either swallowing the liquid that accumulates from a nebulizer or composing viscous slurry with sucralose (Splenda) which is swallowed. Patients are instructed not to eat or drink for 30 minutes after ingesting the medication.

Unfortunately, there are no standard doses or timing of doses (once vs. twice daily) regarding trials with these medications. Viscous budesonide may result in better contact of medication in the esophagus than swallowed fluticasone, which may end up in the mouth or in the lungs [90].

There is ample evidence that topical glucocorticoid therapy is effective in reducing the histological response of EoE. *In vitro* studies in IL-13 stimulated keratinocytes showed a reduction in Eotaxin 3 expression when these cells were treated with fluticasone [91]. Similarly, in a study by Lucendo et al., esophageal biopsies of EoE patients treated with fluticasone showed reduction in IL-5, Eotaxin-1 and Eotaxin- 3 activity [92].

The reduction in immunological activity also appears to affect the downstream complications of fibrosis. Prolonged fluticasone treatment in one study led to a non-significant reduction in sub-

epithelial collagen deposition and significant reduction in CCL18 gene expression, a pro-fibrotic cytokine [93]. More convincingly, a randomized, double blind, placebo controlled trial by Strauman et al., of budesonide over 15 days not only showed significant reduction in eosinophils and alpha tumor necrosis factor, but also significant reduction in lamina propria fibrosis and EGF-beta 1 expression [94].

The problem is that these immunological effects appear not to translate to symptomatic improvement. Early prospective trials of fluticasone with a small number of patients by Arora et al., and Remedios et al., showed universal improvement in symptoms [95,96]. Later studies appear to contradict these impressive results.

The most compelling comes from a randomized, double blind placebo controlled trial of 42 patients given either 880 mcg of flucticasone twice daily vs placebo, showed no difference in dysphagia improvement (57% vs. 33%), despite significant improvement in histology [97]. A recent meta-analysis of topical steroids in placebo controlled trials support the idea that these medicines provide prompt and significant histological response but that symptom relief is less reliable [98].

Other problems may lie in the fact that although the histologic effect of topical steroids is rapid, the long term immunological and fibrotic effect may be diminished in the long term, leading to recurrence of symptoms. In fact, a year-long follow up of patients who initially benefitted from budesonide therapy, showed a regression to higher eosinophil counts and fibrosis scores, as well as no improvement in esophageal thickness [99]. Additionally, the return of symptoms once medication is withdrawn is extremely common. In a 3 year follow up by Helou et al., 91% of patients had recurrence of symptoms after withdrawal of fluticasone treatment, with a mean recurrence time of 8.8 months [100].

This suggests that long term therapy would be needed to consistently control symptoms in patients who have responded to treatment, and raises concern over the side effects of topical glucocorticoid therapy. The short and long side effects of swallowed topical glucocorticoid therapy are unclear at this time, although they appear to be less than systemic steroids. Dry mouth, oral candidiasis (1%) and esophageal candidiasis (up to 30%) have been reported in trials [49].

In addition a case report of herpes esophagitis in a 19 year old woman has been reported [101]. While there are data suggesting long term side effects of inhaled corticosteroids in adults, such as fractures in older patients, pneumonia, and possibly cataracts, there are very little reports for swallowed agents [102]. A concerning finding was recently reported by Golekoh et al., in the Journal of Pediatrics, where 10% of children treated with long term high dose swallowed fluticasone propionate were found to have adrenal insufficiency by a low dose adrenocorticotropic stimulation test [103].

Systemic glucocorticoids

While the effectiveness of systemic steroids has been documented in children, there is a paucity of data in adults. The most revealing study of the benefits and hazards of this treatment method was a randomized open-labeled controlled trial of prednisone 1 mg/kg vs. swallowed fluticasone 110-220 μg four times daily in children. At four weeks, oral prednisone showed a non-statistical advantage in normalization of biopsies (26/32 vs. 18/36). However, overall symptom control was nearly identical and there was no difference in relapse rate or time to relapse seen between the groups. In addition, nearly 40% of the oral prednisone group had systemic side effects including hyperphagia, weight gain and cushingoid features.

The swallowed fluticasone group only documented a 15% esophageal candidiasis rate as a significant side effect [104]. The unacceptable complications of oral prednisone combined with the non- superiority vs. topical gluco-corticoids make systemic steroids, as the ACG guidelines state "reserved for refractory patients or those who need rapid resolution of symptoms" [48].

Acid suppression

Acid suppression has been a frequent medication prescribed for EoE, as a significant amount of patients have responded histologically and clinically [53]. As mentioned earlier, there are studies in adults that show PPI therapy to be effective in reducing clinical and histological symptoms in patient with "EoE phenotype" (50%) and in patient with negative pH monitoring studies (33%) [23].

However, with the advent of the entity known as Proton pump Inhibitor–Responsive Eosinophilic Esophagitis (PPI-REE) the role of acid suppression and PPI is more tenuous in patients diagnosed with EoE using the new guidelines. Still, it is worth noting that PPI's might help reduce the damage of acid on esophageal epithelial cells, which increase permeability and possibly allergen ingestion [24]. PPI's on their own have also been shown to block STAT6, which binds to an eotaxin-3 promoter in esophageal epithelial cells [105]. In addition there are other studies which show that PPI's may have a direct anti-inflammatory effect through the suppression of IL-6, IL-8, alpha TNF production and VCAM-1 expression [106].

Other Medical Treatments, Including Disease Modifying Agents

Other medical treatments targeting different areas in the immune-mediated pathways have been attempted, with varying but overall disappointing degrees of success. A trial of supra-pharmacological doses of montelukast (a leukotriene inhibitor) in 12 adult patients showed symptomatic but no histologic improvement [107], however a similar trial in 11 adult patients showed no benefits on maintaining histological or symptomatic response in patients on swallowed gluco-corticoid therapy [108].The use of biologics appear to be a promising new pharmacological site of regulation of inflammation, however, mepolizumab and relizumab, which target the IL-5 antibody, have shown only histological, but not clinical response in 11 adults and 226 children respectively [109,110]. In contrast, omalizumab, a humanized antibody that binds to IgE and is used in asthma, produced clinical response in 2 pediatric patients but no improvement in histology [111].

A more recent, though less well designed, pilot study in 15 adults appeared to show histological, clinical and endoscopic response at 12 weeks [112]. A small case series of 3 adults showed some clinical and histological response with 6-mercaptopurine/azathioprine [113]. Another drug targeting the Prostagladin D2 receptor has showed small but significant improvement in the histology of EoE patients in a randomized prospective placebo controlled trial of 26 adults [114]. Even more promising data was seen in a recent placebo controlled double blinded study of 23 patients using an intraveous IL-13 blocking drug QAX576, which showed a 2/3 reduction in eosinophil count and a (non-significant) improvement of symptoms (Table 6) [115]. More promising data will be needed before any of these treatment methods are used on a regular basis.

Class	Name	Size of Study (patients)	Symptomatic Response	Histologic Response	Ref
Leukotriene Inhibitor	Montelukast	12	+	-	105
		11	-	-	106
Biologic	Mepolizumab (IL-5)	11	-	+	107
	Reslizumab (IL-5)	226	-	+	108
		pediatric			
	Omalizumab (IgE)	2 pediatric	+	-	109
		15	+	+	110
Thiopurine	6-Mercaptopurine	3	+	+	111
Prostaglandin D2 receptor antagonist	OC000459	26	+	+	112
IL-13	QAX576	23	+	+	113

Table 6: Novel medical therapies for treatment of Eosinophilic Esophagitis.

Dilation

Esophageal Dilation of patients with Eosinophillic Esophagitis has been used extensively over the years. The technique provides definitive treatment for symptoms associated with a narrowed and strictured esophagus, with dysphagia being the most effectively treated. In a meta-analysis by Bohm and Richter of dilation studies performed between 1975 and 2010, 92% of patients had improvement of their dysphagia symptoms [116]. Similarly, in a cohort study of 207 patients, there were significant improvements in dysphagia scores ($P < 0.0001$) and esophageal diameters in all patients. Although 144 of these patients were treated with dilation plus anti-eosinophilic medication (systemic or topical glucocorticoids, leukotriene receptor antagonists, mast cell stabilizers, and/or immune-modulators), these medications did not significantly increase the effectiveness of dilation nor increase the symptom-free duration [117,118]. Unlike the medical and dietary methods mentioned earlier, the effect of the dilation appears to be robust, with 2/3 patients having improvement over 1 year and up to 41% over 2 years [118].

The risk of complication from dilation has always been a concern amongst clinicians treating this disease, especially since early analysis of dilations of 84 adult patients showed a perforation rate of 5% [118]. The fears were based on the theory that the pathophysiological effects of tissue remodeling resulted in mucosal friability, which were supported by the high rate of esophageal tears seen on endoscopy [117]. While post procedure symptoms of chest pain and endoscopic mucosal tears are encountered frequently after dilation, the risk of outright perforation appears to be significantly overstated. A meta-analysis in 2010 of 18 studies encompassing 468 patients showed only one perforation in the 671 procedures performed. Of note, endoscopic mucosal tears were commonly seen in 11/18 of the reports reviewed [118]. Likewise a more recent meta-analysis of 860 patients by Moawad et al. showed only 3 perforations in 992 dilations [119]. In the most recent retrospective cohort study at University of North Carolina, there were no perforations reported among 164 patients who were dilated a total of 486 times [120-124]. Clearly, a better understanding of the disease and refinement of endoscopic techniques have led to much safer outcomes (Table 7).

Patients	Dilations	Perforations
468	671	1 [125]
860	992	3 [126]
164	486	0 [127]

Table 7: Safety of endoscopic dilation in Eosinophilic Esophagitis.

Risk factors for complications include younger age, multiple dilations, upper esophageal strictures, and inability to pass the scope beyond the stricture [125].

Chest pain is frequent occurrence post dilation, with approximately 75% of patients reporting substernal chest pain after the procedure. Despite the frequency of this complication, a survey of 42 patients receiving dilation showed that over 40% of patients had negligible effects and all the patients in the study stated they would have the procedure done again [114]. This data does not serve to trivialize the risks associated with the procedure, but rather to allay the fears of the practitioner from performing this procedure in selected patients who have significant symptoms.

The debate over the best technique to use when performing dilations is not yet solved, partly because of the presentation of the disease. As the effect of the disease is diffuse, there is a need to treat the entire esophagus, which would tend to favor the use of Savary dilators over a guidewire. However Dellon et al., ACG guidelines expressed concerns over this technique regarding sheer forces generated in the previously described fragile mucosa [48]. An apparent compromise between the two methods has been demonstrated by Madanick et al., who demonstrated a method whereby a through the scope balloon is inflated at the GE junction to the estimated diameter of the lumen. The balloon is then inflated and pulled through the esophagus. The process is repeated with an increase in the balloon diameter until an "adequate" diameter is reached. The technique offers the advantage of treating the entire esophagus while being able to directly visualize the process and monitor the mucosal effect of the treatment. In a small group of 13 patients, the procedure proved effective, with 9/13 patients reporting improvement in symptoms. Of note resistance was

encountered in 85% of cases even though narrowing of the lumen was not seen on routine inspection [126].

Although dilation has been shown be very effective in reducing symptoms in patients, it is purely a palliative process. The treatment has been shown to have no effect on the eosinophil counts or other histological aspects of the disease, and symptoms and strictures inevitably return. In addition, a cost analysis model over the course of one year showed an 8% reduction in cost when medical therapy was utilized first over dilation [127].

For these reasons, the ACG guidelines recommend "conservative" dilation in select patients with symptoms that are not improved with medical or dietary therapy or patients with severe stenosis on endoscopy [48].

Endpoints in treatment

It can be difficult to determine what the goals of treatment consist of in EoE, as the outcomes of histological and clinical response have been commonly studied and frequently not correlated. While symptom reduction is obviously extremely important, it should not be the only measure of success of treatment. A recent prospective, observation study of 269 EoE patients showed that symptoms, measured using the validated EoE Activity Index, showed only "modest" accuracy in predicting histologic (62.1%) or endoscopic (65.1%) remission, even when robust cutoff points were used [128].

As in many inflammatory diseases, histological reduction of eosinophils and other inflammatory intermediaries should be a goal, as it is hoped that reduction in the immune medicated response will result in reduction in the often permanent downstream remodeling and fibrosis of the esophagus [48]. New less invasive ways of measuring histological response including the aforementioned tethered confocal endomicroscopy capsule, measuring luminal eosinophil-derived proteins on a swallowed string [129] or a newly developed swallowed, tethered cytosponge, which can provide histological samples, may assist in this measurement [130]. For patients with fibrostenotic disease, esophageal wall distensibility can be followed using a novel technique called impedance planimetry [131] or functional luminal imaging probe (FLIP), in which a bag filled with a solution and passed through the esophagus, measuring both luminal diameter and distensability [132]. These methods, used singly or in combination, May further assist response to therapy and determine whether additional treatment is needed.

Treatment: Conclusions

No one therapy has been proven to be effective in every patient with EoE. Treatment regimens must be tailored to the extent of the disease, the response to therapy, side effects of medications and patient's adherence to dietary restrictions. Patients should be counselled on the effectiveness and the pitfall associated with each treatment method, and a plan involving one of more of these methods should be developed (Table 7). Consensus guidelines exist, but they vary widely in the approach to the disease. As pointed out by Joel Richter in his recent review article, these guidelines are usually based on the experience of a single treatment center [132]. This suggests that local expertise and experience is also an important consideration when implementing a treatment plan (Table 8).

	Symptoms	Histology	Remodeling	Advantages	Disadvantages
Diet	+	+	+/-	-Identifies Allergen(s)	-Nutritional Deficiencies
				-Potential To Prevent Complications	-Multiple Endoscopies Required
				-Long Term Effectiveness	-Cost
					Specialty Foods
					Elemental Diet
					-Requires Strict Compliance
					-Re-sensitization/ Food Allergy?
Topical Steroids	+/-	+	+/-	-Relative Rapid Onset	-Variable Symptom Response Rate
				-Ease of Use	-Candidiasis of Esophagus
				-High Histological Response Rate	-Long Term Effects On GI Tract
					-Long Term Systemic Effects /Safety
					-Long Term Effectiveness Unknown
Dilation	+	-	-	-Highly effective for dysphagia	-Does Not Alter Disease Progression
				-Robust Response	-Expensive
					-Chest Pain, Possible Risk of Perforation

Table 8: Summary-treatment effects, advantages and disadvantages.

Conclusions

The prevalence of EoE has been increasing in the adult population, for reasons not entirely known. Although adults and children likely suffer from the same disease, they present differently due to the delay in diagnosis often seen in adults, which results in more fibrostenotic disease than the inflammatory disease found in children. Proper and accurate diagnosis is essential in establishing the diagnosis of EoE and assisting in treatment of the disease. A combination of dietary, medical and endoscopic treatment is usually needed to treat patients, based on their presentation in the disease course. The goals should be to reduce symptoms and eliminate the immune mediated response, which leads to remodeling and fibrotic disease, which are extremely difficult to reverse once they occur.

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