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New Developments in the Diagnosis, Therapy, and Monitoring of Eosinophilic Esophagitis

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Abstract

Purpose of review Eosinophilic esophagitis (EoE) has transformed over the past two decades from a little-known entity to a significant cause of morbidity in the adult and pediatric population. We reviewed the most recent advancements in the diagnosis, therapy, and long-term monitoring of EoE.

Recent findings Based on clinical, endoscopic, histologic, immunologic, and genetic similarities, there is growing consensus to move away from distinguishing proton pump inhibitor responsive esophageal eosinophilia as an entity distinct from EoE. An increasing number of studies have identified duration of untreated disease as an important determinant of esophageal stricture formation. New approaches to the empiric elimination diet including one, two, four, and step-up protocols were developed to reduce the need for repeated endoscopies during reintroduction of food triggers. Topical steroids remain the mainstay of medical therapy but newer formulations are under development to optimize esophageal delivery. Novel, disease activity monitoring techniques are being evaluated that assess esophageal inflammatory activity without the need for endoscopy.

Summary Understanding of EoE has increased remarkably from the first identification of the disease. The underlying pathogenesis continues to be explored leading to shifts in diagnostic criteria as well as novel therapeutic targets. Innovative methods to monitor disease are under investigation and more research is needed to understand the natural history of EoE.

Introduction

Eosinophilic esophagitis (EoE) is an immune-mediated disease characterized by increased esophageal mucosal eosinophils and esophageal dysfunction. The diagnosis of EoE is based upon clinical presentation paired with increased esophageal mucosal eosinophilia. Although previously considered a rare entity, the incidence and prevalence of EoE have dramatically increased over the past two decades, particularly in reports from the USA and Western Europe. [1] Over this same time period, a growing number of advances have increased our understanding of the clinical features, natural history, and medical/dietary therapy of EoE. This review summarizes recent studies in the field (Fig. 1).

Diagnosis

EoE is defined based on the combination of clinical symptoms and signs of esophageal dysfunction combined with esophageal mucosal biopsies demonstrating ≥ 15 eosinophils/high powered field (eos/hpf) [2]. Current guidelines indicate that prior to making a diagnosis of EoE, other causes of esophageal eosinophilia be excluded, in particular, gastroesophageal reflux disease (GERD) [2–4]. Differentiating between GERD and EoE can be challenging and phenotypic overlap exists [5]. Esophageal eosinophilia was first described as a histologic feature in GERD [6], but later identified in patients with dysphagia without reflux disease [7]. Researchers sought to identify independent predictors of EoE in distinction to GERD which included younger age, atopy, and endoscopic features such as rings, furrows, plaques, and exudates [8, 9]. As the entity of EoE evolved, guidelines incorporated the recommendation for a therapeutic trial of proton pump inhibitor (PPI) therapy for 6–8 weeks in an effort to distinguish distinct entities of GERD and EoE [4]. However, mounting evidence demonstrate that approximately 25–50% of patients with symptomatic, histologic, endoscopic, eosinophil-biomarker, and gene-expression features of EoE respond to PPI therapy calling into question the value of the PPI trial [10]. In 2011, guidelines

Fig. 1. Summary of recent developments in EoE. PPI-REE proton pump inhibitor responsive esophageal eosinophilia, EoE eosinophilic esophagitis.

acknowledged this growing uncertainty by incorporating the concept of "PPI-responsive esophageal eosinophilia" (PPI-REE) [3, 11]. While most data on PPIREE has been in adult cohorts, a recent prospective study of children with esophageal eosinophilia (>15 eos/hpf) also found no differences in atopy, allergy testing, pH testing, and endoscopic scores in patients with PPIREE compared to patients traditionally labeled as EoE [12]. Together, these recent studies support a paradigm shift to remove the criteria of failed PPI response prior to establishing a diagnosis of EoE and the inclusion of PPI-REE as true EoE [13, 14]. The diagnostic criteria for EoE still centers on typical clinical presentation including symptom presentation and endoscopic findings, which should minimize the risk of incorrect inclusion of GERD. Patients with a GERD phenotype (dominant heartburn, erosive esophagitis, abnormal pH testing) with esophageal eosinophilia would still be appropriate for a PPI trial prior to consideration of EoE-specific therapy. Furthermore, given the high population prevalence of GERD, overlap between GERD and EoE is inevitable.

Natural history

EoE emerged as a rare disease in the 1990s [7] and now serves as a significant cause of GI morbidity. Annual costs in the USA related to EoE are estimated at nearly 1.4 billion dollars [15]. Previous studies have found EoE in over 10% of patients presenting with dysphagia [16]. With its growing recognition, the incidence of EoE has been estimated at a rate of 3.7/100,000 persons/year by one recent study [17]. The rise in disease patterns has been postulated to be related to environmental changes over the past decades and is supported by twin studies [18].

Although EoE has a rising incidence and prevalence, the disease is still considered relatively new and long-term data are few. Nevertheless, increasing data support the chronicity of EoE with propensity for progressive esophageal remodeling resulting in stricture formation. In a prospective randomized, placebo-controlled, 50-week maintenance study of budesonide by Straumann et al., patients in the placebo group had an expected increase in esophageal eosinophilia but also recurrent dysphagia and an increase in subepithelial fibrosis [19]. This data supports retrospective studies that identified that longer duration of untreated EoE was associated with increased risk of esophageal strictures. Schoepfer et al. showed that strictures were seen in up to 39% of patients with a diagnostic delay of over 8 years and 70% with a delay of greater than 20 years [20]. New technology, known as the functional lumen imaging probe (FLIP), measures distensibility of the esophagus during volumetric distention. FLIP technology has been applied to the evaluation of the function and anatomy of the esophagus with a growing number of studies in EoE [21–24]. Recently, FLIP has been used in the pediatric population to highlight decreased distensibility in EoE patients. Those with higher eosinophil counts and lamina propria fibrosis had decreased distensibility leading to the concept that EoE can affect distensibility in children with EoE [25]. Carlson et al. identified

that medical and dietary therapy significantly improved esophageal distensibility in 44% of adults with EoE, supporting the concept of reversibility of remodeling in EoE [26•].

Therapy

While diet, medications, and esophageal dilation remain effective therapies for EoE, recent advances are evaluating the efficacy of topical steroids optimized for esophageal delivery and biologic therapies targeting specific allergic pathways involved in the pathogenesis of EoE.

Diet

Elemental formula therapy for EoE was first described in the study by Kelly et al. in 1995 and remains the most effective diet therapy for EoE [27]. In spite of this, elemental diets have not been widely adopted due to poor patient compliance and palatability. Conceptually, given the antigen-mediated nature of EoE, allergy testing-directed elimination diets have been explored. However, studies to date have demonstrated a limited response to allergy directed therapy in adults with EoE [28–30].

Empiric elimination diets targeting the most common food triggers related to EoE remain a more practical and effective option with 50–57% histologic response. The six-food elimination diet (SFED) that eliminates milk, egg, soy, wheat, peanuts/tree nuts, and fish/shellfish was first described in pediatric and subsequently adult EoE [29, 31]. Eliminating six major food categories can be difficult for patients and reintroduction can be challenging, taking several months and requiring multiple endoscopies. Given the high presence of milk, soy/legumes, egg, and wheat to be identified as the food trigger for EoE patients [29, 32, 33], a four food elimination diet (FFED) has been reported [34]. In Molina-Infante et al.'s study of the FFED, about half of patients achieved clinical and histologic remission [34]. All patients only had one or two identified food triggers, most commonly milk. The patients who did not respond to the FFED were offered the SFED and one-third of these patients then achieved remission. Given the possibility of "step-up" therapy, a recent study by the same group utilized a novel "step-up" approach eliminating milk and gluten first and then advancing to a FFED followed by SFED for non-responders (2-4-6 diet) [35]. This incremental approach offered the advantage of reduced utilization of endoscopy during the reintroduction process.

The long-term effectiveness of diet therapy has been poorly studied. A prospective Spanish study reported a sustained histologic response for over 2 years but in only 15 adults [32]. A recent retrospective study of 52 adults treated with an elimination diet reported that about half of the patients who initially responded continued to maintain response with a mean follow up of 2 years [36]. In patients willing and able to continue avoidance of identified food trigger(s), diet elimination retained effectiveness. However, when factoring the reported lower than expected induction response of 40% (21/52), long-term histologic response to diet therapy was achieved in only 19% (10/52) of the cohort. Thus, the majority of patients either did not respond to diet or lost

response over time due to diet non-adherence, indicating a considerable limitation to use of diet therapy for maintenance of EoE.

Corticosteroids

Swallowed, topical steroid therapy is the most commonly used therapeutic approach in EoE, providing direct effect to the mucosa and minimizing systemic side effects of systemic steroids. As no medication has been approved by the US or European regulatory authorities for indication of EoE, topical steroids are being used off-label. Moreover, currently used formulations designed for asthma, especially using a metered dose inhaler, present challenges in terms of administration. Recent clinical trials have utilized steroid formulations optimized for esophageal delivery. A recent phase two randomized, double-blind, placebo controlled trial of budesonide oral suspension demonstrated significant improvement in dysphagia symptom scores, histologic findings, and endoscopic features [37•]. Importantly, this study was the first to demonstrate improvement using validated patient reported outcome and endoscopic scoring instruments. In a European study, Miehlke et al. studied two budesonide formulations in a randomized, double-blind trial [38•]. Here, patients were randomized to treatment with a budesonide tablet, budesonide viscous suspension, or placebo. Histological remission and improvement in endoscopic scores was found in all budesonide groups as compared to placebo after 2 weeks of therapy.

Recent studies have raised concerns regarding the long-term effectiveness of topical steroids in adults with EoE. A retrospective study reported that 50% of adult patients with EoE had loss of response to steroids by 18.5 months and 75% by 29.6 months [39]. Similarly, a Swiss prospective study of budesonide demonstrated a loss of initial histologic response in 64% at 1 year follow up [19]. Most recently, a prospective, multi-center, open label study of budesonide oral suspension found that 58% of initial histologic responders lost their response at 24 week follow-up [40•]. All three studies attributed part of the loss of the steroid induction response to steroid dose reduction during maintenance phase, but more data is needed to clarify if steroid tolerance may develop in EoE.

Biologics

Addressing the allergic pathogenesis of EoE, several trials are evaluating the efficacy of novel biologic therapies targeting inflammatory cytokines. Interleukin-5 (IL-5) is involved in the activation and release of eosinophils from the bone marrow [41] and has been studied in hypereosinophilic syndromes and allergic asthma [42]. Mepolizumab, an anti-IL-5 immunoglobulin, was recently studied in pediatric EoE in a randomized trial by Assa'ad et al. Patients received one of three doses of mepolizumab every 4 weeks for three infusions. Peak eosinophil counts were less than 20/hpf in 32% of patients [43]. Another randomized controlled trial of mepolizumab in adult EoE supported these findings with reduction in mean eosinophil counts [44]. Interleukin 13 (IL-13) is an additional cytokine identified in higher expression in esophageal biopsies from patients with EoE. [45] Rothenberg et al. studied the use of anti-IL-13 therapy, QAX576, in patients with EoE [46]. Patients received QAX576 or

placebo for 8 weeks. The primary endpoint of a decrease of 75% of peak eosinophil counts was not met, although mean counts did decrease by 60%. This improvement continued for 6 months after cessation of active therapy [46]. Another anti-IL-13 therapy, RPC4046, has also been shown to significantly decrease eosinophil counts and improve endoscopic features as compared to placebo [47]. Most recently, interleukin-4 (IL-4) has also been shown to have increased expression in patients with EoE [48]. A study of dupilumab, an antibody targeting signaling of both IL-4 and IL-13, is currently undergoing in patients with EoE. Preliminary reported data demonstrated improvement in dysphagia scores, endoscopic signs, and peak eosinophil counts with the use of dupilumab [49]. While many promising studies are searching for additional biologic targets, the long-term data on these agents are not known in EoE. It also remains unknown how biologic therapy will be positioned in patient management decisions. Postulated advantages of this form of therapy include avoidance of daily steroid administration, systemic effects that benefit multiple forms of allergic disease in highly atopic individuals, application for steroid refractory patients, and ability to improve esophageal remodeling.

Dilation

Dilation provides a direct approach to improve esophageal luminal diameter and decrease symptoms of dysphagia and risk of food impactions. As described earlier, progression of EoE and remodeling can lead to stricture formation [20, 50]. Food impaction and dysphagia are leading causes of morbidity in patients with EoE. Once fibrostenotic features have developed, it is unclear how effectively medical therapy can improve or reverse the process without dilation, although a recent study noted improved esophageal distensibility with medical therapy in the absence of esophageal dilation [26•].

Several studies have examined the safety and effectiveness of dilation therapy. A recent meta-analysis reviewed 845 EoE patients who underwent 1820 esophageal dilations [51]. Symptoms improved in over 95% of patients. Mean pre-dilation stricture measurements were 9.9 mm and post-dilation measurements were 16 mm. Patients on average underwent three dilations, however, this number widely varied from 1 to 35 dilations per patient. Perforation, the most worrisome complication of dilation, was seen in 0.38% of patients (7/1831). Other major complications including hemorrhage (0.05%) and hospitalization (0.67%) were uncommon. This large scale meta-analysis highlights both the efficacy and safety of dilation therapy [51]. It should be noted that this data was almost exclusively based on retrospective studies from centers focusing on esophageal disorders. Estimates of complication rates need to acknowledge potential variation based on the experience in diverse practice settings. Ultimately, it would be the hope of all EoE therapy to halt the progression to fibrostenotic features and reduce the need for dilation.

Disease monitoring

Primary disease therapeutic endpoints in EoE are grouped into clinical, histologic, and endoscopic outcomes that were recently reviewed in a conference

sponsored by the American Gastroenterological Association with participation of the FDA and industry [52•]. Historically, patient-reported symptoms have not correlated well with disease activity such as esophageal eosinophil density [53]. Scoring tools have been developed to assess patient symptoms and are currently used in clinical studies including the Dysphagia Symptom Questionnaire (DSQ) and EoE Activity Index (EEsAI). With novel endoscopic evaluation tools such as the EoE Endoscopic Reference Score (EREFS) [54], features of EoE can now be more categorically represented. While a reproducible and objective outcome, there is considerable variability in what defines histologic response in terms of eosinophil density. The recent development of a more comprehensive histologic scoring tool (EoE-HSS) appears promising in terms of validation characteristics and ability to provide a more comprehensive assessment of a broader range of pathologic features in EoE [55•].

Esophagogastroduodenoscopy (EGD) is an important modality for diagnosis and monitoring of disease. Given that many patients present with dysphagia, EGD is needed to obtain biopsies as well as rule out diagnoses aside from EoE. While EGD is often required in the initial work up of patients, guidelines do not specify the interval at which to perform follow-up endoscopic evaluation. The timing of repeat EGD is generally determined on a case by case basis, although commonly performed 2–3 months following a therapeutic intervention. Although a primary monitoring method, EGD carries high costs and remains an invasive procedure requiring sedation.

Newer, less invasive technologies are being developed to assess disease activity. In 2012, researchers studied the use of an esophageal string test to measure eosinophil-derived proteins in luminal secretions. Protein levels correlated with eosinophil counts and could distinguish between active EoE, GERD, and normal controls [56]. A study by Kern et al. highlighted the ability of cytologic brushings to be used [57]. Compared to esophageal biopsy, the sensitivity and specificity of brushings was estimated at around 70% both proximally and distally. The concept of collecting superficial cells has also previously been studied in Barrett's esophagus [58]. Similarly, in EoE, the Cytosponge device (Medtronic) has been investigated. The Cytosponge is a device contained within a dissolving capsule. Patients swallow the capsule which then expands into a small mesh sponge after the outer gelatin shell dissolves. The sponge is connected to a string and then withdrawn from the oral cavity as it samples esophageal cells. Studies using the cytosponge in EoE patients have shown a sensitivity of 83% and a specificity of 57% [59]. A more recent study showed a slightly lower sensitivity of 75% and a higher specificity of 86% of the Cytosponge device [60••]. Both studies used the same cutoff of 15 eosinophils/hpf for disease activity, but the latter examined nearly five times the number of paired samples. Though all three of these new technologies are less invasive, structural changes of EoE are not assessed.

Transnasal endoscopy (TNE) has been developed and now studied in EoE as an alternative to traditional endoscopy. TNE does not require sedation and can be done in the outpatient clinic. TNE has previously been compared to EGD and shown to be a safe technique [61]. In the pediatric EoE population, TNE has been used for monitoring and obtaining esophageal specimens for eosinophilic analysis [62]. Parents in this study largely preferred TNE to EGD.

As mentioned previously, FLIP technology has now been used to investigate distensibility characteristics of patients with EoE. Higher severity of rings

according to the EREFS score correlated with lower distensibility measures of remodeling by FLIP [63]. The FLIP catheter is passed through the oropharynx for measurements during routine endoscopy. Specialty centers are currently evaluating this technology as an adjunct to traditional endoscopy [24].

Conclusion

Knowledge regarding EoE has grown markedly over the past two decades. Initially a disease seldom encountered, EoE is now widely recognized as a common cause of esophageal symptoms in children and adults. Much has been learned about EoE and its distinction and overlap with an even more common disorder, GERD. Studies have highlighted the chronicity of disease and progression to fibrostenosis. With the understanding of EoE as an immune-mediated disease, therapies are targeted to eliminating antigen exposure through diet and decreasing the inflammatory response with steroids and biologic therapies. The long-term management of EoE is evolving. Patients and physicians both realize the cumbersome nature of repeated EGDs and newer, less invasive technologies are being studied. EoE remains an evolving entity and more is yet to be discovered about this young disease.

Compliance with ethical standards

Conflict of interest

Ronak Vashi Patel declares no conflict of interest.

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Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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