

New diagnostic and therapeutic frontiers in eosinophilic esophagitis

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Eosinophilic esophagitis (EoE) is a relatively new disease that is increasingly recognized as a chronic inflammatory condition with currently evolving diagnostic and therapeutic aspects. There is data to support the rising prevalence of EOE especially in western countries. EoE is an emerging cause of dysphagia and food bolus impaction in adults as well as abdominal pain, feeding disorders, and gastroesophageal reflux-like symptoms in younger patients. EoE is ever more recognized as a separate disease process that is more complicated than eosinophilic infiltration from gastroesophageal reflux disease. Food and environmental antigens both play significant roles in stimulating T-helper (Th-2) inflammatory response. Current therapeutic options include use of proton-pump inhibitors, immunosuppressive drugs, elimination diets, and esophageal dilatation. Simple elimination of food and environmental antigen exposure can be challenging in adults due to the difficulty in accurately identifying triggering antigens and adherence to restrictive diets from a wide range of putative food allergens. Novel therapeutic options are being presented as potential treatments that target chemokines and specific immunologic mechanisms for EoE. This review will aim to summarize the latest and evolving approaches to EoE diagnosis and management. In the future, biomarkers of inflammatory response may help diagnose, treat, and stratify individual patients for better treatment outcomes with this chronic disease.

KEY WORDS: Eosinophilic esophagitis - Gastroesophageal reflux - Allergens - Inflammation.

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Eosinophilic esophagitis (EoE), a disease that was first reported in 1978, is one of the leading causes of dysphagia in adults.¹ It is characterized by eosinophilic infiltration in the squamous and deeper layers of the esophagus. Aside from dysphagia, EoE manifestations vary with patients' age. Other symptoms associated with EoE include food impaction, pyrosis, non-cardiac chest pain, and odynophagia.² Approximately, 15% patients undergoing upper gastrointestinal endoscopy for dysphagia and up to 50% of adults with food impaction that requires endoscopic retrieval have EoE.³⁻⁵

The American Gastroenterological Association first presented their guidelines for the diagnosis of EoE only in 2007.⁶ This by itself was a major landmark in the diagnosis of EoE as there was no previous attempt to standardize the case definition for EoE.⁷ Previous studies had variable criteria which would have impeded significant strides in defining EoE and determining its pathogenesis and treatment options. The current consensus recommendations for EoE were updated in 2011.⁸ EoE is now clearly defined as a clinicopathologic disease which requires: 1) symptoms related to esophageal dysfunction; 2) >15 eosinophils/high

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power field in at least one esophageal biopsy; 3) eosinophilia limited to the esophagus; and 4) exclusion of other causes of esophageal eosinophilia, specifically proton pump inhibitor (PPI)-responsive esophageal eosinophilia (PPI-REE).⁸ The phenomenon of PPI-REE, acknowledged by the recent guidelines, represents the coexistence of gastroesophageal reflux disease (GERD) with EoE. This gives rise to the controversial role of PPI in EoE therapy. Despite the attempt to formulate a consensus in the diagnosis of EoE, there is still continued variability in both clinical practice and research literature. These differences present on-going challenges in analyzing the outcomes of different studies on EoE treatment strategies. We anticipate as more information is gathered on the pathogenesis and natural history of EoE that these guidelines will continue to evolve similar to any disease entity that is experiencing greater clinical recognition and increasing burden of disease.

Epidemiology and natural history of EoE

The epidemiology of EoE varies widely depending on the study population. As a new disease, reports of EoE were predominantly single patient reports and case series during the first two decades of its recognition as a distinct disease entity. Initially, there was more literature available in the pediatric population from which adult gastroenterologists have continued to extrapolate data for clinical and investigational application. Data from our own Olmsted County in Minnesota estimate a prevalence of 0.055% in a span of 30 years.⁴ Other studies have suggested a wide range of estimates from 0.002% up to 0.4%, per population-based studies conducted in Switzerland and Sweden, respectively.^{9, 10} In spite of these differences, the predominance of male patients seems to be consistent across different study population. There is a 3-to-1 ratio between males and females diagnosed with EoE in most studies.^{11, 12} This

gender predisposition offers an interesting observation that may someday be elucidated with on-going research on genetic and epigenetic abnormalities in EoE.

It is known that patients with EoE have alterations in a large series of genes.¹³ Eotaxin-3, a principal mediator in the allergy pathway, has been shown to be overexpressed in EoE patients.¹⁴ It will be fascinating to speculate how specifically these genetic abnormalities may be associated with gender and racial differences. In terms of race, there is increased prevalence among Caucasians as compared to other ethnic groups.¹⁵ A retrospective analysis of EoE patients at a major referral center did not show any significant racial differences in most clinical parameters except that Caucasians were much older at the time of presentation and were likely to have esophageal rings on endoscopy.¹⁶ The reasons for these disparities are not clear. It is likely that large scale studies will be needed before a clear understanding of these likely racial disparities can be clarified. A major challenge in such studies is the identification of racially-diverse participants who would have similar environmental and food exposures in order to eliminate several confounding factors aside from race and gender.

Prospective studies evaluating the natural history of EoE are also limited. There are only two published studies on the natural history of EoE.^{17, 18} The first prospective study to describe the natural history of EoE had 30 patients, followed for 11 years.¹⁷ Many of the patients diagnosed in the past 3 decades had symptoms for years before being diagnosed with EoE. This prolonged course underlines the chronicity of this disease. In our prospective cohort, 51 adult patients demonstrated 63% recurrence after completing a 6-week treatment of fluticasone with a mean follow-up of three years. Relapse of symptoms and inflammation occur after cessation of treatment which support need for long-term management in some patients with EoE.

Like any other chronic disease, EoE remission can also occur as a part of a fluc-

tuating disease course. As more patients are diagnosed and treated, large scale prospective cohorts are being organized in different centers to assess the natural history of EoE and possible effect of therapy with different strategies. There are retrospective analyses of pediatric patients treated with EoE in recent literature.^{19, 20} In a 10-year retrospective analysis of children with EoE, relapse of symptoms and inflammation was evident after treatment cessation.²⁰ This observation is no different from what we see in our adult population. There are several important questions that could be answered by studying prospective pediatric cohorts. It is not clear whether pediatric EoE cases persist or re-occur in adulthood. It will be interesting to know if successful treatment in childhood would attenuate any future risk of recurrence. Although we do not have sufficient epidemiologic data yet, it is our contention that EoE being a chronic allergic condition will be a recurrent condition in some patients who are genetically and environmentally-predisposed to have recurrence of disease throughout their lifetime.

Emerging concepts in EoE pathophysiology

The development of EoE is likely brought about by a complex pathway of genetic and epigenetic alterations that trigger an abnormal allergic response. The initial inciting event is currently thought to be primed by an extra-esophageal allergic exposure. In laboratory mouse models, *Aspergillus fumigatus* exposure through the nasopharyngeal airway has been shown to induce esophageal eosinophilia.²¹ Indoor allergens such as cat, dog, cockroach, and dust mites have also been demonstrated to be potent inducers of esophageal eosinophilia.²² Other experiments have suggested the induction of a T-helper-2 response (Th2) by esophageal epithelial cells.^{23, 24}

With activation of Th2, potent cytokines are produced. Consequently, cytokines IL-13 and IL-5 are found to be elevated in

EoE patients.^{25, 26} By itself IL-13 has been shown to induce esophageal eosinophilia by intratracheal administration of IL-13 in experimental setting.²⁵ On the other hand, IL-5 overproduction by circulating T cells may also be instrumental in recruiting eosinophils from the bone marrow in response to antigen recognition in the esophagus.²⁷ The identification of IL-13 and IL-5 can serve either for diagnostic or therapeutic targets in the future. Recently recognized biomarkers include eotaxins-1, 2 and 3 which are secreted by esophageal epithelial cells to attract eosinophils. Interestingly, eotaxin-3 also increases in response to IL-13 and IL-5.^{14, 28} As such, eotaxin-3 has been shown to be elevated in EoE. There is data to suggest IL-13-driven epithelial cell response to be associated with marked gene dysregulation including eotaxin-3 overproduction.²⁶ Once eosinophils have been engaged, there is a series of esophageal eosinophilic degranulation resulting in multiple proinflammatory mediators such as major basic protein, eosinophilic cationic proteins, and other neurotoxins and peroxidases.²⁹ To add to the complexity of this pathway, eosinophils also augment the allergic cascade by exposing food allergens to dendritic cells that exacerbate any concurrent antigen-specific Th2 response.

Mast cells are also a major component of this inflammatory cascade. Similar to eosinophils, they also produce several inflammatory cytokines. In addition to elevated eosinophils counts, the density of mast cells are reported to be elevated in esophageal biopsies of EoE patients.^{30, 31} The identification of mast cells has been the target of therapy as there is evidence to support reversibility of mast cell-associated production in patients being treated with fluticasone.³²

Most of the current literature on the pathogenesis of EoE has focused on the different components of this inflammatory pathway. In the future, we would expect further delineation of subtle relationships between cytokine and cellular components of the EoE inflammatory pathway. Novel drugs will likely target several components

of this complicated system to control ongoing inflammation. The direction of EoE research is currently on identifying genetic and epigenetic aberrancies that either activate or fail to suppress the recurrent inflammatory cascade brought about by an inciting allergic exposure.

The gene coding for eotaxin-3 is the first functional genetic abnormality identified from a large transcriptome described in EoE patients. Recently, variations at chromosome 5q22 have been associated with regulation of Th2 responses.³³ Other abnormal genes have been also described that affect B cells, tryptase expression, and IgE receptors.^{26, 32, 34} There is data also to support increased expression of mast cell genes in patients with EoE, resulting in an intensified inflammatory response.³⁵

Not only are there genetic associations to some of the inflammatory markers, there is also evidence to suggest contribution of genes that code for filaggrin, a regulator of cellular junctions.²⁶ Tight cellular junctions are believed to prevent inadvertent food antigen exposure to the antigen-presenting cells in the esophageal mucosa that may trigger an allergic reaction. More interestingly, the application of steroids has been shown to restore filaggrin levels. With these exciting findings, we anticipate more genetic variations being proposed to explain the heightened inflammatory response. However, the main challenge is to find a common link to all of the abnormal genetic findings, allergic pathways, and clinical manifestations in EoE.

Frontiers in EoE diagnosis

The current diagnostic guidelines for EoE require a set of clinicopathologic criteria which implies the need for both symptomatic and histologic features to be present. We previously cited these specific guidelines in our introduction. We think that these guidelines will continue to evolve as we advance our understanding of EoE. For most adult patients presenting with dysphagia, upper gastrointestinal endoscopy has been the initial step taken by most gastroenterologists in diagnosing these patients. However, there is no single pathognomonic feature diagnostic of EoE. There is a wide variation of endoscopic findings such as edema, furrowing, and presence of white exudates Figure 1. The different non-specific findings highlight the limitations of using endoscopic features alone for the diagnosis of EoE.

Biopsy sampling is indicated in patients with dysphagia especially when EoE is suspected. The value of biopsies lies in finding eosinophils which are not found in normal esophageal mucosa.³⁶ Nevertheless, eosinophilic infiltration is not solely sufficient to make the diagnosis of EoE. It is a non-specific feature because its etiology cannot be ascertained based on microscopy. A Swedish population-based study estimates that 5% of the population may have non-specific esophageal eosinophilia but only 1% may have probable to definite EoE.¹⁰ The recently-recognized phenomenon of PPI-REE and other conditions that cause esophageal eosinophilia must be ruled out before di-

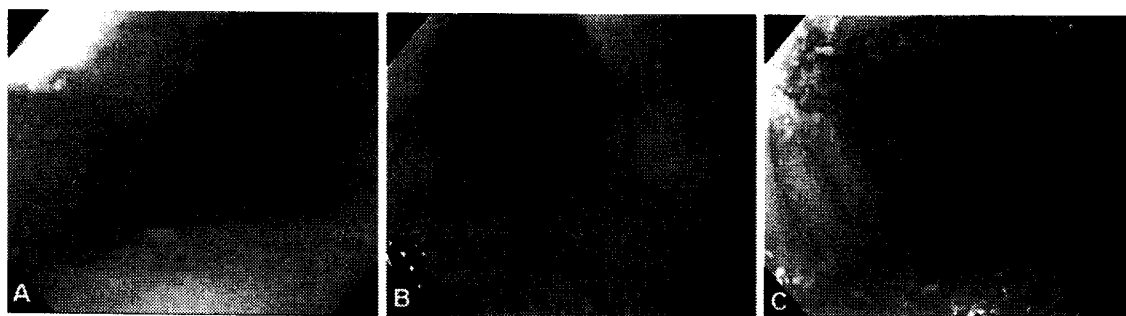


Figure 1.—Endoscopic findings in EoE. (Panel A) moderate inflammation, (Panel B) inflammation with longitudinal furrowing, (Panel C) severe inflammation with esophageal rings and white exudates.

agnosing EoE. These include GERD, eosinophilic gastroenteritis, hypereosinophilic syndrome, infection, Crohn's disease, and connective tissue disorders.^{6, 8}

The density of eosinophilic infiltration is crucial in the current diagnostic criteria for EoE. The quantification of eosinophils is dependent on the size of each relative high-power-field (hpf) that may vary from one microscope to another.³⁷ Random sampling during biopsy may also result in variations in eosinophil counts which may fall below the threshold of the current diagnostic criteria. Thus, it is not unexpected to find studies that report increased yield of eosinophil detection after repeated sampling.³⁸ In the absence of significant eosinophilic infiltration, extracellular eosinophil-derived neurotoxins have been demonstrated in patients with EoE by immunofluorescence. This may suggest the possibility of eosinophilic degranulation that may not be detected during routine histopathologic processing and microscopic examination.³⁹ In addition to eosinophils, other inflammatory cells such as mast cells may also be seen on biopsy. It is not clear if the detection of other inflammatory cells and eosinophil-derived products may increase the current accuracy of microscopic diagnosis for EoE.

Allergy testing can be an adjunct in EoE management. At least 60% of children with EoE with have at least one identified food allergen on skin prick testing.⁶ As such, skin prick testing for foods and environmental allergens has been recommended in pediatric EoE patients to identify potential allergens and atopic status. Atopy patch testing, a specialized tests available in select referral centers, may also be used in conjunction with the skin prick test. Although neither of these tests are specific for allergens that drive EoE, the avoidance of allergens identified on skin prick test and atopy patch testing may help resolve EoE manifestations in two thirds of pediatric EoE patients.⁴⁰ In adults, the recognition of food allergies by skin testing is not well studied. In one study of 23 adults, 19 (82%) were detected to have serum IgE for one or more food allergens.⁴¹ Wheat, tomatoes, carrots, and onions were identified

to the most common food items. However, 17 (74%) of these patients also had multiple sensitivity to other environmental antigens.

Other emerging tests that may be applied to the diagnosis of EoE include eotaxin and basophil histamine release assays. As we previously mentioned, eotaxin is a signaling peptide that plays a significant role in eosinophil recruitment. Detection of increased levels of serum and tissue eotaxin and has been demonstrated in EoE patients.¹⁴ Treatment with topical steroids may down-regulate its expression.⁴² Although eotaxin assays may potentially be used in the detection of EoE activity, its fluctuating levels in response to allergen exposure and withdrawal may make it unreliable in monitoring response to therapy. Another investigational test is the basophil histamine release assay which detects histamine release after exposure to allergic triggers.⁴³ This test relies on the affinity of basophils to IgE receptors that stimulate histamine release after binding of an inciting allergen. The limitations of this test include possible non-specific reaction to allergens that may not necessarily induce esophageal inflammation in addition to the lack of test standardization at present time.

Current and emerging treatments of EoE

The main strategies in treating EoE comprise of diet, drugs, and dilations; the so-called 3Ds.⁴⁴ There are on-going developments on all three strategies which in one way or the other address specific pathophysiologic mechanisms of EoE. In this review of current and upcoming treatment strategies for EoE, we will focus on the rationale for using these different pharmacologic agents and their current controversies. A discussion on dietary therapy and endoscopic management of EoE merits an entirely separate treatise.

Proton pump inhibitors

Proton pump inhibitors (PPIs) are both important and yet controversial in the man-

agement of EoE. They can both be used as either a diagnostic test to differentiate GERD, PPI-REE to that of actual EoE. In addition, there is also significant overlap of GERD in patients with EoE.^{8, 45} As a result, the resolution of esophageal symptoms with PPI may be either be due to the successful treatment of either GERD or EoE itself. There have been a few case series reporting resolution of symptoms in patients diagnosed with EoE after treatment with high dose PPI for at least two months.^{5, 46} One of the larger retrospective analysis of patients with ≥ 15 eosinophils per hpf had 36 study participants who underwent high dose PPI therapy for three months that resulted in 14 (39%) patients to demonstrate histologic response by reduction of esophageal eosinophilia to ≤ 5 eosinophils per hpf.⁴⁷ The responders were classified as nonallergic eosinophilic esophagitis. As such, the use of PPI has been proposed as an initial diagnostic and therapeutic approach to differentiate patients whose symptoms and histologic findings are due to EoE from those with non-EoE conditions. In a randomized trial of 25 patients with EoE, treatment with omeprazole 40 mg daily was compared to fluticasone 440 mcg twice daily. This study showed no significant difference in symptomatic or histological response.⁴⁸ In our opinion, PPI will remain as an initial strategy for differentiating other conditions that have eosinophilic esophageal infiltration. The role of PPI in EoE will continue to evolve but there will always be the certainty that patients who respond to PPI will need continued surveillance as they may relapse and manifest with eventual EoE symptoms and histologic findings.

Topical corticosteroids

Topical corticosteroids are regarded as the foundational therapy for EoE. They are relatively safe except for some cases of oral and candidal esophagitis which could be avoided with oral rinsing after each treatment. Much of the experience in using topical steroids comes from the pediatric literature. The use of swallowed fluticasone was

first reported in 4 children with EoE who had clinical improvement.⁴⁹ Subsequent studies in adults have shown improvement in symptoms with the use of different treatment schedules including fluticasone 220 μg /puff twice daily for six weeks or 250 μg /puff twice daily for a total of four weeks.⁵⁰ Viscous budesonide is another alternative to patients who have difficulty in swallowing aerosolized fluticasone. The rates of remission are similar to fluticasone.⁵² Attempts to increased esophageal delivery of topical corticosteroids have been reported. An example is the use of an oral gel with budesonide and a mucosal adherent, rincinol. Sixteen EoE patients were treated with this oral gen containing budesonide 3 mg twice daily for a week. At the end of the treatment, all patients reported at least a 75% improvement in dysphagia with half of the participants reporting complete resolution.⁵³

Similar to other treatment options with EoE, the use of topical corticosteroids is not without controversy. In a double-blind, randomized, placebo-controlled trial of fluticasone in 42 adult EoE patients treated with either aerosolized fluticasone 880 μg twice daily or placebo inhaler twice daily for 6 weeks; aerosolized, swallowed fluticasone demonstrated histologic but not symptomatic response.⁵⁴ The primary end point of complete symptom response was not statistically different between those on fluticasone (43%) and placebo (29%). The secondary outcome, histologic response by a reduction in esophageal eosinophilia greater than 90%, was achieved in 62% of patients on fluticasone as compared to 0% on placebo ($P < 0.001$). Unlike earlier uncontrolled trials, the data from this randomized study have raised concerns about the efficacy of topical steroids in treating esophageal symptoms. The results show that topical steroids clearly reduce esophageal eosinophilia. In contrast, relief of esophageal symptoms may be more difficult to demonstrate. Until more data from prospective randomized studies are available, treatment follow-up based on patients' general symptoms with or without histologic response

may need to be individualized. It is possible that histology alone is not the best indicator of successful treatment response.⁵⁵ In this regard, there is a need for better biomarkers of response than simple quantification of esophageal eosinophilic infiltration.

Systemic corticosteroids

Similar to topical steroids, systemic corticosteroids were first reported in a series of 20 children with presumed eosinophilic esophagitis who were treated with oral methylprednisolone at a dose of 1.5 mg/kg/day divided into twice daily doses for a total of four weeks.⁵⁶ Clinical and histologic improvement was demonstrated in all but one patient. After a 12-month follow-up, only 10 (50%) patients remained asymptomatic. While effective for induction, the relapsing course of EoE and the need for minimizing exposure to systemic corticosteroids make it difficult to manage patients on systemic steroids alone. Since 2007, the practice guidelines have restricted the use of systemic steroids to patients in whom urgent symptom relief was required. This patient population was defined as those with severe dysphagia resulting in dehydration and malnutrition as well as those with severely inflamed esophagus with small caliber and tight strictures that are high risk for endoscopic dilation. The future goal of current pharmacologic research in EoE is to identify other agents that are safe for long-term use without the significant side effects of systemic steroid use.

Emerging therapies

Montelukast, a leukotriene receptor antagonist, selectively blocks the leukotriene D₄ receptor which serves as a chemotactic factor for eosinophils.⁵⁷ With the goal of decreasing esophageal eosinophilic burden, montelukast was initially considered as an ideal pharmacologic agent for EoE. In a series of 8 EoE patients dysphagia treatment with montelukast, incremental dose escalation from 10 mg/day up to a maximum dose of 100 mg/day resulted in initial symp-

tom resolution in six patients.⁵⁷ However, all patients reported clinical relapse after discontinuation of montelukast or reduction of dose below their maintenance dose. There were also side effects including nausea, headache, and myalgias. A recent prospective, cross over study between topical corticosteroid and fluticasone in adult EoE patients demonstrated that montelukast was inferior to fluticasone in maintaining symptomatic and histological response.⁵⁸ More studies will be needed to identify the potential use of montelukast and the subset of EoE patients who may benefit from this leukotriene receptor antagonist.

Anti-IgE antibodies are currently prescribed for severe persistent allergic asthma. Clinical trials have successfully demonstrated reduction in eosinophils in the lungs and the peripheral circulation with omalizumab, an anti-IgE antibody. There is a report of two patients with multiple food allergies and EoE on a very restrictive diet who have been treated with omalizumab.⁵⁹ The regimen with omalizumab only showed remission in esophageal symptoms without histologic improvement. At this time, there are no published clinical trials on other anti-IgE agents.

Antagonists to T-helper type 2 cell receptors have also been tested. The premise is that blockage of the chemoattractant receptors in T-helper type 2 cells will inhibit allergic reaction by downgrading prostaglandin D₂ driven chemotaxis. A placebo controlled trial of 26 adult EoE patients treated with a chemoattractant receptors antagonist in T-helper type 2 cells only demonstrated reduction in eosinophil count without improvement in symptoms.⁶⁰

The current frontier in pharmacologic development for EoE is to find molecular targets after modest success in preliminary studies on receptor antagonists. Current potential targets based on our understanding of EoE pathogenesis include IL-5, IL-13, and eotaxin. Anti IL-5 agents, mepolizumab and reslizumab, were studied in case series of patients who were unresponsive or dependent on systemic steroids. IL-5 is responsible in eosinophilic recruitment.

As such, the humanized antibodies against IL-5 have been used in hypereosinophilic syndromes. Stein *et al.* first reported the use of mepolizumab in four patients who demonstrated combined symptomatic and histologic improvement.⁶¹ A more recent randomized, placebo-controlled, double-blind trial of 11 EoE patients demonstrated modest symptom improvement without any significant statistical difference with mepolizumab, compared to placebo.⁶² The same modest results are reported with reslizumab. In a large scale double-blind, randomized, placebo-controlled trial of 226 patients; reslizumab significantly reduced esophageal eosinophilic burden but there was no improvement in symptoms as compared to placebo.⁶³ Whether anti IL-5 agents will gain any more momentum in being proposed as novel pharmacologic agents for EoE is uncertain at this time.

Preclinical trials are also in progress for antibodies directed against IL-13, another cytokine in the allergic pathway of EoE. Investigators have proposed using an anti-IL-13 agent to reduce circulating IL-13, which is overexpressed in EoE.⁶⁴ IL-13 is partly responsible for inducing the Th2 pathway in EoE pathogenesis. Humanized anti-eotaxin antibody, CAT-213, is also being tested.⁶⁵ Eotaxin, a signaling peptide in esophageal epithelial cells, has the capability of attracting eosinophils. Reduction in eotaxin levels may reduce eosinophilic burden in the esophagus. To date, there is no published clinical trial on anti-eotaxin therapy for EoE. We will anticipate the results of these studies in the hope of finding more effective therapies with enduring outcomes.

Conclusions

EoE is an emerging chronic allergic disease of the esophagus which has now become a common cause of dysphagia in adults. As further advances in the diagnosis and treatment of EoE are made, it is becoming more evident that EoE is a chronic relapsing disease. Various strategies are being developed to identify putative allergic

processes that trigger the development of EoE in contrast to non-specific eosinophilic infiltration of the esophagus. The long-term medical management of patients with EoE refractory to standard therapy still remains to be defined. Several of the diagnostic and therapeutic aspects of EoE presented in this review remain at the forefront of clinical practice and research. After 3 decades of recognizing this disease, there is still much to be understood regarding its pathophysiology, diagnosis and optimal therapy. This becomes more challenging when one considers the parallel changes in our environment, food exposures, and ever changing patient demographics.

Riassunto

Nuove frontiere diagnostiche e terapeutiche dell'esofagite eosinofila

L'esofagite eosinofila (EOE) è una malattia relativamente nuova, sempre più riconosciuta come una patologia infiammatoria cronica, con aspetti diagnostici e terapeutici attualmente in evoluzione. Ci sono dati a sostegno della crescente prevalenza dell'esofagite eosinofila soprattutto nei paesi occidentali. L'esofagite eosinofila è una causa emergente di disfagia e di occlusione da bolo alimentare negli adulti, così come di dolore addominale, disturbi alimentari e sintomatologia simile al reflusso gastroesofageo nei pazienti più giovani. L'esofagite eosinofila è sempre più riconosciuta come un processo patologico separato, più complicato dell'infiltrazione eosinofila della malattia da reflusso gastroesofageo. Gli antigeni alimentari e ambientali svolgono entrambi un ruolo importante nella stimolazione della risposta infiammatoria del linfocita T (Th-2). Le attuali opzioni terapeutiche comprendono l'uso di inibitori della pompa protonica, farmaci immunosoppressori, diete di eliminazione e dilatazione esofagea. La semplice eliminazione dell'esposizione ad antigeni alimentari e ambientali può essere difficile negli adulti, a causa della difficoltà di identificare con precisione gli antigeni di attivazione e del rispetto delle diete restrittive per una vasta gamma di allergeni alimentari putativi. Le nuove opzioni terapeutiche sono state presentate come potenziali trattamenti che mirano alle chemochine e a meccanismi immunologici specifici per l'esofagite eosinofila. Questo articolo ha lo scopo di riassumere gli approcci più recenti e in evoluzione per la diagnosi e la gestione dell'esofagite eosinofila. In futuro, i biomarcatori di risposta infiammatoria potranno contribuire a diagnosticare, trattare e stra-

tificare i singoli pazienti per migliorare i risultati del trattamento di questa malattia cronica.

PAROLE CHIAVE: Esofagite eosinoflica - Reflusso gastroesofageo - Allergeni - Infiammazione.

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