Unmet Therapeutic Needs in Eosinophilic Esophagitis

Seema S. Aceves

Division of Allergy, Immunology, Department of Pediatrics and Medicine, University of California, San Diego,
Rady Children's Hospital, San Diego, Calif., USA

Key Words

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Abstract

Eosinophilic esophagitis (EoE) is a clinicopathologic disease of increasing prevalence in children and adults worldwide. EoE is defined by a robust, acid-resistant, often panesophageal eosinophilia. Disease complications include food impactions and strictures. While much has been learned since it was first described in the late 1970s, there are still a number of unmet clinical needs. This review provides an overview of these and addresses our current state of progress in meeting these challenges. The best diagnostic criteria, the least invasive mechanisms for procuring tissue, the best therapeutic intervention, and an understanding of how therapies affect EoE natural history remain to be systematically addressed. In addition, the classification of EoE subjects by phenotype, genotype, and/or endotype is required but dependent upon further large-scale systematic studies.

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As a disease in its relative infancy, eosinophilic esophagitis (EoE) has a number of unmet disease and patient needs. These needs begin with the very basic, i.e. the agreed upon diagnostic criteria, and extends into more

complex issues of FDA approval of medications, natural history, the need for interventions, patient symptoms and the alignment of symptoms with disease activity, and pharmacogenomics.

Unmet Diagnostic Needs

Consensus recommendations, based on the collective expert opinion of pediatric and adult gastroenterologists, allergists, and pathologists, are that EoE diagnosis rests on tissue histology of ≥ 15 eosinophils per high-power field on a hematoxylin and eosin stain of an esophageal biopsy specimen at its most inflamed area and from any portion of the esophagus along its length [1]. This is a more clear diagnosis when made in the presence of 'high-dose' acid blockade, i.e. twice-daily proton pump inhibitors (PPIs) [1–3]. However, these diagnostic criteria are imperfect in that they are derived by expert opinion rather than being evidence based. Currently, the best histologic criteria in addition to or outside of eosinophils are not clear. Disease management requires repeated tissue assessment in order to confirm the state of disease activity since there is no clear alignment of patient symptoms with disease activity and no surrogate disease markers [4, 5]. In children, endoscopy requires general anesthesia and can pose a significant patient burden due to repeated invasive procedures and its associated costs and parental

concerns [6]. As it currently stands, there are no histologic, endoscopic, or symptom-based features that are pathognomonic for EoE [1].

The relationship between EoE and other eosinophilic gastrointestinal disorders is not entirely clear. However, esophageal involvement can clearly occur in other eosinophilic gastrointestinal disorders such as eosinophilic gastroenteritis (EGE) [7, 8]. It is important to note that this constitutes EGE with esophageal involvement and does not meet the diagnostic criteria for isolated EoE. While it has been reported that subjects with EoE can have gastric eosinophilia [7], in our experience this is often a transient phenomenon with spontaneous resolution. Whether concurrent gastric eosinophilia has an impact on EoE natural history, response to therapy, or disease progression needs further defining.

Since recurrent endoscopy and biopsy poses a significant healthcare and patient burden, one pressing need is for less invasive diagnostic modalities for EoE. Less invasive tests include the novel application of a previously used test for giardia called the 'string test' [9]. In this case the subject swallows a string for a few hours or overnight, and eosinophil products are assayed from the proximal, middle, and distal portions of the string. The levels of major basic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase all correlate strongly to the numbers of eosinophils seen on biopsy specimens taken at the time of string removal [9]. In addition, the esophageal string test can be used to procure experimental specimens such as those for assessing the EoE microbiome [10]. Another potential noninvasive technique was recently reported that documents the use of technetium-labeled heparin. The initial studies have been done in vitro to assess eosinophilia using EoE biopsies [11]. However, since this label can be used in vivo, this technique holds promise as a noninvasive EoE diagnostic measure. Lastly, a device known as 'endoFLIP' can be used to assess EoE features that are not readily assessable using current techniques, specifically esophageal rigidity, a feature that is thought to reflect esophageal remodeling [12]. Importantly, it has been shown that the severity of esophageal remodeling correlates to the risk of food impactions [13]. In contrast to these tissue-based techniques, investigations into finding peripheral surrogate disease markers in either blood or stool have not been successful [14].

Although eosinophils are used as the ultimate diagnostic criteria, EoE is associated with a robust inflammation that includes mast, CD3+, CD8+, and B cells. Studies have shown that using mast cell tryptase can increase the diagnostic sensitivity and specificity for EoE [15, 16]. In-

deed, mast cells have significant functional effects in EoE [17]. A molecular profiling platform that has high sensitivity and specificity for active and treated EoE and which assesses 96 genes that have disrupted transcription in EoE has been recently described and may have wide applicability [18]. This platform was also utilized in formalin-fixed archived specimens which broadens its ability to be used either retrospectively or as part of general clinical practice. In addition, techniques that detect eosinophil products in the absence of intact eosinophils may add sensitivity to EoE diagnostics [19]. Although important and of significant potential impact, these new techniques are currently limited for use in studies at research centers. In addition, the cost of these techniques may limit their use for a number of years. Since hematoxylin and eosin is globally used to assess eosinophilia, one important aim would be to investigate if composite indexes that combine histologic, symptom, and endoscopic findings can increase the diagnostic sensitivity and specificity of EoE. To this end, current research trials are underway to analyze the relationships between the components of tissue histology, endoscopic findings, and patient symptoms.

There have been a number of recent studies that have evaluated and even validated scoring tools for endoscopic and symptom features in EoE, including quality of life [20–22]. The next important undertaking will be to correlate the results of these tools, and subcomponents of these tools, systematically to EoE disease activity. The need in this area is particularly great since United States federal funding agencies are focused on the use of patient-reported outcomes (symptoms and quality of life) as an important metric for therapeutic success [23, 24]. Whether clinically based tools are sufficient in isolation to gauge therapeutic response or if they can be used reliably as a component of a composite disease activity index that includes histology remains to be seen.

Unmet Clinical Needs

Allergy Testing

Current allergy testing for food triggers in EoE has had variable results depending on the food and the type of testing utilized. In children, combined skin prick and patch-based diets have provided moderate success rates (50–60%), but preliminary data in adults shows very low success rates for predicting allergic food triggers using these tests [25–28]. Many questions remain in EoE, including proof of antigen-specific T cells. In addition, the timing and whether there is an immunologic shift in the

reaction during its disease course is not clear. It is possible, for example, that an esophageal food reaction begins as an antigen-specific response, but then shifts to an innate response as inflammation is perpetuated. An alternate pattern is also possible with a shift from innate to adaptive immunity [29, 30]. These unanswered immunologic questions in combination with the delayed effects of foods in EoE necessitate a need for new allergy testing modalities to find the antigenic triggers for EoE.

Current data from adults with EGE shows that there are food-specific T cells in the peripheral blood of these patients [31, 32]. Consistent with the potential IL-5-dependent and IgE-independent disease mechanism for eosinophilic gastrointestinal diseases, EGE subjects have food-specific T cells that produce IL-5 in contrast to food anaphylactic subjects in whom food-specific T cells produce IL-4, an interleukin which is important for class switch to IgE [31, 32]. When cultured, IL-5+ cells require longer time frames and chromatin remodeling in order to develop, which is consistent with the chronic nature of the EoE disease process [32]. If present in the periphery of EoE subjects, these cells could provide insight into disease pathogenesis and provide a potential surrogate allergy marker.

Personalized Medicine: Therapeutics and Genotype-Phenotype Interactions

Current regimens of topical corticosteroids and dietary elimination are successful therapeutic options in the majority of pediatric and adult EoE patients [28, 33–36]. Indeed, disease resolution can occur in relatively short time periods from 15 days up to 3 months. Only one adult study has looked prospectively at maintenance therapy using lowered budesonide doses in a placebo-controlled trial [37]. Such studies have not been completed in pediatric subjects. As such, the possibility of lowering the dose of a successful medication regimen and the duration of such therapy is not clear. In addition, the utility of therapies that combine diet and medications has not been evaluated.

Although dietary elimination is largely successful with empiric food elimination having success rates from 50 to >70% in both children and adults [28, 36, 38, 39] and testing-based diets having success rates from >50 to >70% among pediatric subjects [26, 27], the ability, order, and timing of food reintroduction remains unclear. In addition, the natural history of food sensitization and reactions in EoE are not clear. Pediatric studies show that <10% of children regain the ability to eat all of the foods eliminated from their diets [40]. However, the clinical

characteristics that align with successful food introduction remain elusive and there are currently no predictive indexes for therapeutic success or failure for either diet or medications.

Genetic indexes that could predict EoE risk and response to treatment would be of significant impact since evaluation of therapeutic response depends on repeat esophagoduodenoscopy and biopsy. We have had a number of insights into the genetics of EoE. The thymic stromal lymphopoietin gene and its receptor appear to be risk factors for EoE, as do polymorphisms in the eotaxin-3 gene [41–43]. In addition, a polymorphism in the TGF- β 1 gene can correlate with therapeutic response to topical corticosteroids as well as fibrotic severity [33, 44, 45]. Interestingly, a recent report demonstrated that subjects with connective tissue diseases had higher rates of EoE, and it is important to note that both Marfan syndrome as well as Loeys-Dietz syndrome are associated with mutations that increase TGF- β 1 expression and signaling [46, 47].

Despite these advances, there are many aspects of EoE that need clarification before true genetic risk indexes or disease prediction indexes can exist. First, an understanding of the genetics of disease risk and disease modification studied in large cohorts of subjects is required. In addition, an understanding of both treatment response as well as natural history in those subjects who are not treated, who chronically fail therapy, or who are nonadherent to therapy is necessary. Lastly, the impact of environmental exposures on allergic diseases can be substantial and, in the case of EoE, the ‘environment’ constitutes not only physical aspects such as the pollen season but also foods. Indeed, environmental risks require further defining. In addition, it will be important to know if certain alleles in risk and/or disease-modifying genes have similar effects by race, ethnicity, and age of EoE subjects.

EoE disease phenotypes are becoming apparent, but much remains to be understood. When thinking about phenotypes, one could categorize them in a number of ways which can include: response to therapy (e.g. corticosteroid nonresponders vs. responders), triggers (e.g. diet and/or pollen induced), continuity of symptoms (e.g. transient vs. intermittent vs. chronic), and complications (e.g. fibrotic or stricturing). Although clinically these phenotypes are emerging in the literature, the molecular associations of genotype with phenotype need further elucidation. This is important as the molecular mechanisms and polymorphisms in the responsible genes may have significant predictive value. Lastly, if there are distinct categories of disease pathology, categorization by endotype may be useful [48].

Perhaps the best currently defined phenotype is that of the fibrotic EoE subject. In adult patients, especially those who have prolonged (>20 years) untreated disease, the natural history seems almost uniformly to be towards stricture progression with >70% of the subjects having strictures at the time of diagnosis [49]. The severity of the strictures can vary from those that restrict passage of the endoscope but do not require dilation to those that are long segment, difficult to dilate, and associated with bleeding, tearing, and perforations. The majority of adult subjects with an evaluable lamina propria had fibrosis with more than one third having mild to moderate fibrosis which correlated with the finding of esophageal stricture [49]. Nine percent of the subjects had severe fibrosis and 20% had an intermediate- to high-grade stricture [49]. In children who are nonresponders to topical budesonide, the presence of lamina propria fibrosis is unchanged or progressive with nonresponders generally comprising approximately 20% of the population in children <10 years of age and 50% in children >10 years of age [33, 44]. The genotypic, environmental, and racial features that could influence fibrosis remain to be understood.

In the context of disease response, perhaps the most complex of the potential EoE phenotypes is 'PPI-responsive esophageal eosinophilia'. Our studies have demonstrated that a subset of PPI-responsive subjects progress to having EoE despite continued treatment with twice-daily PPIs. Often, the clinical assumption is that when eosinophilia responds to PPI therapy, the cause is acid and the subject has gastroesophageal reflux disease. However, high-dose PPIs can have anti-inflammatory effects that include decreasing vascular activation for eosinophil trafficking and transmigration [50]. In addition, in vitro studies have demonstrated that PPIs decrease the expression of EoE-associated chemokines such as eotaxin-3 [51]. Given these findings, it is very likely that at least a subset of PPI-responsive esophageal eosinophilia subjects, which is estimated at about 15% in children [27], simply have a PPI-responsive variant of EoE [3, 52]. It is of particular clinical importance to better define these subjects since it is vital to continue to follow them to see if they have recrudescence of esophageal eosinophilia with an ultimate diagnosis of EoE.

Understanding Natural History and Medication Side Effects

One pivotal question in EoE therapeutics is whether treatment can alter the natural disease course towards strictures. It will be important to assess if those subjects who do not respond to therapeutic interventions and

have sustained esophageal eosinophilia go on to have worsening fibrosis and strictures. It is equally important to determine if dietary or medication treatment of subjects who have esophageal strictures decreases their need for esophageal dilation and/or diminishes the risk, recurrence, or progression of existing strictures. The imperative issue to address herein is whether management in general or the aggressiveness of inflammatory control can alter the natural history of EoE.

Although asthmatic subjects have been treated with long-term inhaled corticosteroids, the possible effects of prolonged topical corticosteroid use in EoE is not known. In addition, prolonged PPI use can associate with bone demineralization [53]. A study of asthmatic children treated with PPI as adjunctive asthma management had higher rates of fractures than their placebo-treated counterparts [54]. Answers to this question of bone density is particularly important in EoE subjects where diet is being manipulated and in which food avoidance by children is often intrinsic to the disease. Certainly, the avoidance of cow and soy milk, two common sources of calcium, could decrease adequate calcium intake. In addition, low levels of vitamin D have been associated with food allergies and asthma, and as such the interplay between calcium, vitamin D, and EoE may be of significant importance to understand [55, 56].

Conclusions

There are a number of unmet needs in EoE. These include assessing the best diagnostic criteria, the least invasive diagnostic modality, the categorization of subjects into varying phenotypes, the association of these phenotypes with genotypes, the natural history and whether treatment changes its course, and the side effects of dietary changes and medications. The answers to these questions will rely on collaborative efforts among researchers and clinicians caring for EoE subjects and may alter the diagnostic framework and treatments for EoE. As such, although we have accumulated substantive information about EoE, a significant amount of work remains to be completed in order to meet the clinical needs of patients.

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