

Journal Pre-proof

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PII: S1081-1206(19)31465-6

DOI: <https://doi.org/10.1016/j.anai.2019.12.003>

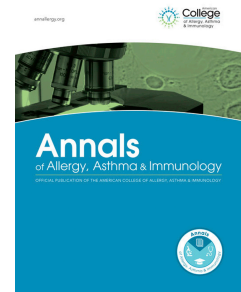
Reference: ANAI 3095

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 3 October 2019

Revised Date: 25 November 2019

Accepted Date: 2 December 2019



Please cite this article as: Nhu Q, Aceves SS, Unanswered Questions in Eosinophilic Esophagitis, *Annals of Allergy, Asthma and Immunology* (2020), doi: <https://doi.org/10.1016/j.anai.2019.12.003>.

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Unanswered Questions in Eosinophilic Esophagitis

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Funding Sources: NIH/NIAID AI092135 (S.S.A.), NIH/NIAID AI135034 (S.S.A.), NIH/NCATS L30 TR002507 (QMN), U54 AI117804 (S.S.A, Q.M.N.)

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COI: Dr Aceves is a co-inventor of oral viscous budesonide patented by UCSD and licensed by Shire-Takeda Pharmaceuticals. Dr Aceves is an author for Up-to-Date, has research funding from Ferring Research Institute and is a consultant for Regeneron, Astellas, Gossamer Bio, and Alimmune pharmaceuticals.

Acknowledgement: Dr. Nhu has fellowship support from CEGIR. CEGIR (U54 AI117804) is part of the Rare Disease Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), NCATS, and is funded through collaboration between NIAID, NIDDK, and NCATS. CEGIR is also supported by patient advocacy groups including American Partnership for Eosinophilic Disorders (APFED), Campaign Urging Research for Eosinophilic Diseases (CURED), and Eosinophilic Family Coalition (EFC).

Word count: 1006

Eosinophilic esophagitis (EoE) is an antigen-driven disease associated with a patchy, pan-esophageal infiltration of eosinophils, mast cells, and T cells. Persistent inflammation triggers dysregulated wound healing that progresses to pathologic tissue remodeling with esophageal rigidity and clinical symptoms of dysphagia and food impactions.¹ The most common complaints in adults and teenagers is dysphagia while younger children more commonly have symptoms that mimic gastroesophageal reflux disease like vomiting. The disease pathogenesis is similar in children and adults with higher rates of strictures and endoscopic remodeling in adults which may be due to distinctions in pathogenesis or longer disease duration. The natural history of untreated or therapy unresponsive EoE is to stricture formation.

Deciphering patient specific EoE triggers

Milk, egg, wheat, and soy are the main EoE triggering foods.² However, due to the lack of adequate testing modalities to decipher triggering foods, a one-size-fits-all modality of food elimination has been utilized. This has proven inefficient since patients must undergo repeated endoscopy with biopsy each time a new food is added into the diet. Skin prick, serum IgE and atopy patch testing have failed to consistently identify triggering foods. Novel testing modalities are direly needed. Currently, IgG4 and milk-specific T cells have been identified in EoE patients. These tests may offer new mechanisms to determine EoE triggers in the future.

EoE can exacerbate in the relevant pollen season. Aeroallergens can be demonstrated to deposit directly in the diseased esophagus and murine models support the ability of aeroallergens to be isolated triggers for EoE.³ EoE patients have higher rates of oral allergy syndrome, suggesting that there may be a mechanistic cross-reactivity between the foods and pollen that trigger EoE.³ While such cross reacting antigens would be clear for foods such as wheat, they are less clear for other common EoE food triggers such as milk and egg. The utility

specific immunotherapy using standard or component derived antigens as an adjuvant therapy remains to be understood, although a handful of reports suggest its utility.³

One obstacle to deciphering the triggering antigens in EoE is the paucity of research supporting the presence of antigen-specific T cells. Current data show lack of esophageal T cell diversity in active EoE, suggesting a restricted antigen repertoire in EoE T cells.⁴ Indeed, the esophageal signal in EoE has a significant innate component with elevated IL-1, IL-33, TSLP, and ILC2s. Elucidating the central pathogenic cell(s) driving EoE is a key unanswered question in the field and understand this would potentially lead to new diagnostic and therapeutic modalities.

Choosing patient-specific therapies- personalized medicine in EoE

Accepted modalities to induce EoE remission are high dose PPI, topical corticosteroids, and elimination diet.⁵ The question of which modality to initiate has centered on the patient's choice and medical recommendations based on clinical presentation. For example, a child with failure to thrive and gastroesophageal reflux symptoms merits a PPI trial and elimination diet should be used cautiously to avoid limiting caloric intake. In contrast, a patient with a stricture may require systemic corticosteroids plus PPI for gastric protection and therapeutic dilation. Studies suggest that PPI-responsive EoE is a milder variant of EoE, that therapeutic response may be transient, and that patients with single nucleotide polymorphism (SNP) rs1059513 in the STAT6 gene may be more likely to respond to PPI.⁶ In contrast, patients who are high CYP2C19 rapid metabolizers and/or have allergic rhinitis are more likely to break through PPI. Disease relevant gene SNPs may help to guide a molecular or endotype-based therapeutic strategy. For example, mutation in the TSLP gene could trigger a more restrictive elimination diet; SPINK7 mutation could trigger protease inhibitor therapy;⁷ and TGF- β 1 promoter mutations could trigger combination therapy of topical corticosteroids and anti-fibrotic agents. Recent studies revealed distinct EoE molecular phenotypes using the EoE diagnostic panel (EDP) which could be insightful for endotype-based therapies.⁸

Sustained response to therapy seems to be a requirement to avoid esophageal rigidity and loss of luminal diameter. Currently, the only predictors of sustained response are female sex and initial response to therapy.⁹ Baseline dilation was determined recently to be the only independent predictor of non-response.¹⁰ Gauging disease severity is also a challenge since eosinophilic inflammation does not uniformly align with esophageal rigidity. To this end, there may be epithelial markers that accurately assess remodeling severity, potentially obviating the need for lamina propria or tissue rigidity measures.¹ Determining the clinical and genetic factors that contribute to disease susceptibility, disease exacerbation, and treatment response would allow for optimization of disease prevention and treatment planning.

Targeting disease complications- fibrosis and remodeling

While EoE patients with remodeling features including fibrostenosis have difficult to treat disease, this patient population has the fewest potential interventions. There is a pressing need for novel adjunctive anti-fibrotic therapy in EoE. This could come in the form of biologics or by repurposing existing medications with inherent anti-fibrotic activities such as thiazolidinediones (Nhu, Aceves et. al, DDW 2019). Understanding the factors that predispose to more severe or rapidly progressive EoE are a significant need. The persistent activation of fibroblasts after resolution of inflammation and the ability of fibroblasts and smooth muscle cells to respond to rigid environmental cues are concerning for structural cell memory of the diseased environment.¹

Elucidating the best endpoints

EoE is considered a chronic disease that requires chronic maintenance therapy. However, the extent of chronic eosinophilic control required to avoid complications is not clear. Since current natural history studies are up to 10-15 years, it remains unclear if there are subsets of patients who outgrow their disease over >15-20 years. Current studies also are

75 biased by patients who return for follow up. It is possible that those who are lost to follow-up
76 have EoE remission.

77 There is a need for endpoints in addition to endoscopy. Complications to decision-
78 making include reports that chronic EoE is not always continually symptomatic, making it difficult
79 to gauge when therapy should be held and restarted without invasive procedures. Less invasive
80 tools such as the esophageal string test and cytosponge are promising.

81 *Conclusions*

82 We have made many strides in EoE. However, many significant unmet needs remain.
83 These include FDA approved therapies for patients in the U.S., novel anti-fibrotic therapies,
84 testing modalities that accurately gauge EoE triggers and severity, and understanding the best
85 therapeutic endpoint that represents optimal disease control to alter the natural history to
86 stricture formation. Ongoing investigations are likely to yield answers to these pressing
87 questions, hopefully soon.

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