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To treat or not to treat: The minimally symptomatic EoE patient

Amanda Muir, MD^{1,2}, Hillary Moore, MD^{1,2}, and Jonathan Spergel, MD, PhD^{1,3}

¹Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104 USA

²Division of Pediatric Gastroenterology, Hepatology, and Nutrition, The Children's Hospital of Philadelphia, Philadelphia, PA 19104-6160

³Division of Allergy and Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA 19104 USA

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disorder in which a mixed inflammatory cell infiltrate leads to symptoms of esophageal dysfunction. While great strides have been made to understand the pathophysiology and natural history of eosinophilic esophagitis over the last 30 years, there still does not exist an FDA-approved therapy. Current therapeutic strategies involve empiric elimination of likely allergenic triggers or swallowed topical steroid preparations or proton pump inhibitors (PPI).^{1–2} Diet therapy whether by empiric or allergy testing identified often involves avoiding foods ubiquitous in the western diet such as milk, wheat, soy and egg.³ Patients are required to cease eating all or some of these food groups at the same time and subsequently undergo serial endoscopies as foods are re-introduced. Elimination of dietary triggers can successfully lead to resolution of symptoms and histologic findings ranging with an overall 72% efficacy and testing directed diet being 46%³ to 95% with elemental diet^{1–3}.

Like dietary elimination, topical steroid therapy may also be successful in resolving symptoms and histopathology¹. Despite some therapeutic success, the mode of ingestion is cumbersome, with some patients swallowing fluticasone puffs or others making a viscous slurry (mixing with Splenda, apple sauce, honey, etc) with improvement of symptoms and histology ranging from 50 to 80%. Similarly, studies have suggested that chronic use of topical steroids may contribute to growth suppression and adrenal insufficiency⁴.

Disease response to both of these therapeutic options has been promising. However, with this success, comes a large burden of therapy. In addition to lifestyle and medication side effects, both therapeutic strategies involve multiple endoscopies with general anesthesia.^{1–3} Concerns regarding adverse effects of both types of therapy have led practitioners to ask: if patients have only minimal symptoms, do we still need to treat?

Part of the answer lies in the fact that there is often discordance between symptom severity and biologic disease activity (endoscopic/ histologic findings).⁴ The most common symptoms in pediatric EoE are vomiting and feeding refusal, and in older children and adults are dysphagia and food impactions. To cope with these symptoms, individuals with EoE have developed behavioral adaptations, both conscious and not. These include avoidance of certain textures, slow eating with prolonged chewing, and excessive water intake during meals. Thus, an individual who has made unconscious lifestyle modifications may not report symptoms of EoE, but may in fact have active endoscopic or histologic disease.

Many studies have shown that symptoms and disease activity do not correlate.⁵ Standardized and validated tools to assess disease activity are scarce. In adults, a number of instruments have been developed in the past decade most recently, the Eosinophilic Esophagitis Activity Index (EEsAI) Patient-Reported Outcome (PRO) in order to determine the correlation between symptoms and endoscopic and histologic disease activity. Evaluation of these tools has shown that correlation between symptom severity and biologic disease activity is unreliable with an overall accuracy of detecting endoscopic and histologic remission based on a distinct score cutoff value was only modest (area under the curve between 0.6 and 0.7). Thus, endoscopic and histologic remission cannot reliably be identified by symptoms alone⁴.

In pediatrics, correlating symptoms and disease activity is even more challenging. Young children may not be able to accurately verbalize symptoms. Symptoms such as feeding difficulty may not improve even in the setting of disease remission if the child has developed aversions and behavioral issues around food. Therefore, as in adults, symptoms do not necessarily correlate with disease activity. Similar symptom scoring systems have been established including, the validated PEES v2.0⁵, a scoring system that takes into account patient-perceived symptoms as well as parental report by proxy. Evaluation of PEES v2.0 showed that there was no statistically significant correlation between symptoms and esophageal eosinophil count or the inflammatory transcriptome characteristic of EoE disease activity.

This discordance between symptom severity and disease activity becomes important clinically because untreated disease can have consequences, specifically, progression to fibrosis. Fibrosis is the most devastating consequence of long-term esophageal inflammation, involving excessive deposition of collagen leading to esophageal stiffening. Endoscopically, fibrosis appears as a ringed/trachealized esophagus or global esophageal narrowing and stricture. Symptomatically, fibrostenosis can present as dysphagia, delayed transit of food, and frequent food bolus impactions. Epidemiologic studies have revealed that EoE is a progressive fibrostenotic disease⁶, meaning that the longer there is untreated disease, the more likely fibrostenotic features and stricture will develop. Dellon in his study noted that for every 10 years of age at diagnosis, the odd ratio increases 2-fold for strictures and 7-fold for dysphagia.

Halting the development of fibrosis is the primary reason to aggressively treat EoE. While there may be no symptoms reported at the time of diagnosis, as fibrosis develops symptoms may evolve from vomiting to dysphagia and endoscopies may then be accompanied by

dilations⁶. Recent publications have shown that there is decreased esophageal distensibility- as measured by the diameter of the esophagus at certain pressures- in the EoE esophagus compared to control⁷. Thus, even in the pediatric population that has relatively fewer years of disease chronicity, there is still a measurable difference in esophageal distensibility⁷. Furthermore, the inactive pediatric population with EoE had significantly greater esophageal distensibility compared to patients with active disease and longitudinal studies in adults show that both diet and topical steroids improve esophageal distensibility⁸. Thus, decreasing disease activity can positively affect esophageal health. Therefore, EGD should be done when there is a change in therapy or symptoms with a goal of getting the eosinophil count as low as possible minimum of less than 15/high power field.

If there is already fibrostenosis, is it too late for medical therapy? Extrapolating from other organ systems such as the liver and skin, fibrosis is irreversible. Once there has been collagen deposition, it cannot be removed from the tissue. However, a recent study from Runge et al has shown that therapy improves outcomes, even in the fibrostenotic population⁹. And in pediatric patients, treatment response to steroids demonstrated improved histologic fibrosis scores². Patients with fibrostenosis that achieve remission have fewer dilations compared to those with ongoing disease activity. Taken together, these data along with the distensibility data suggest that treatment can improve outcomes in the inflammatory as well as the fibrostenotic patients.

While the burden of EoE therapy may be great, the burden of active EoE is also great. Social pressures can make diet elimination stressful and there is anxiety surrounding potential contamination. However, there is also stress surrounding ongoing active disease. Is food going to get stuck at my work event? Am I going to vomit at school? Studies have shown that active disease strongly correlates with a worse quality of life¹⁰. The goal of therapy for the minimally symptomatic patient (symptoms not affecting the daily quality of life) should be to avoid progression to fibrostenosis and maintain minimal symptomatology so as to maintain enhanced quality of life and improved natural history⁶⁻⁸. Thus, multiple factors including esophageal endoscopic appearance, histology, distensibility and patient overall quality of life must be considered in addition to symptoms when deciding whether a minimally symptomatic patient should be treated.

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Table 1

Reasons to treat
<ul style="list-style-type: none">• Preserve esophageal function• Prevent progression to esophageal fibrosis• Improved quality of life

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