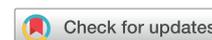


Pro/Con Debates

Minimally symptomatic patients with eosinophilic esophagitis should still be actively treated-PRO



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Eosinophilic esophagitis (EoE) is a chronic immune-mediated disorder in which a mixed inflammatory cell infiltrate leads to symptoms of esophageal dysfunction. Although great strides have been made to understand the pathophysiology and natural history of EoE during the last 30 years, a US Food and Drug Administration–approved therapy still does not exist.

Current therapeutic strategies involve empiric elimination of likely allergenic triggers, swallowed topical steroid preparations, or proton pump inhibitors.^{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 reintroduced. Elimination of dietary triggers can successfully lead to resolution of symptoms and histologic findings, with an overall efficacy of 72% and a testing-directed diet rate of 46%³ compared with 95% with an elemental diet.¹⁻³

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Like dietary elimination, topical steroid therapy may also be successful in resolving symptoms and histopathologic findings.¹ 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 histologic findings ranging from 50% to 80%. Similarly, studies have suggested that long-term use of topical steroids may contribute to growth suppression and adrenal insufficiency.⁴

Disease response to both these therapeutic options has been promising. However, with this success comes a large burden of therapy. In addition to lifestyle and medication adverse 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 whether patients with only minimal symptoms still need to be treated.

Part of the answer lies in the fact that there is often discordance between symptom severity and biologic disease activity (endoscopic and histologic findings).⁴ The most common symptoms are vomiting and feeding refusal in pediatric EoE and dysphagia and food impactions in older children and adults. To cope with these symptoms, individuals with EoE have developed behavioral adaptations, both conscious and not. These behavior adaptations 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 found 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 Patient-Reported Outcome, 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 only a modest overall accuracy of detecting endoscopic and histologic remission based on a distinct score cutoff value (area under the curve between 0.6 and 0.7). Thus, endoscopic and histologic remission cannot reliably be identified by symptoms alone.⁴

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 Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) version 2.0,⁵ a scoring system that takes into account patient-perceived symptoms and parental report by proxy. Evaluation of PEESS version 2.0 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 that leads to esophageal stiffening. Endoscopically, fibrosis appears as a ringed or 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 disease,⁶ meaning that the longer there is untreated disease, the more likely fibrostenotic features and stricture will develop. Dellon et al⁶ 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. Although 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 dilations.⁶ Recent publications have reported that there is decreased esophageal distensibility, as measured by the diameter of the esophagus at certain pressures, in the EoE esophagus compared with control.⁷ Thus, even in the pediatric population that has relatively fewer years of disease chronicity, there is still a measurable difference in esophageal distensibility.⁷ Furthermore, the inactive pediatric population with EoE had significantly greater esophageal distensibility compared with patients with active disease, and longitudinal studies in adults found that both diet and topical steroids improve esophageal distensibility.⁸ Thus, decreasing disease activity can positively affect esophageal health. Therefore, esophagogastroduodenoscopy should be performed when there is a change in therapy or symptoms with a goal of getting the eosinophil count as low as possible (minimum of <15 eosinophils per 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 al⁹ found that therapy improves outcomes, even in the fibrostenotic population. In pediatric patients, treatment response to steroids demonstrated improved histologic fibrosis scores.² Patients with fibrostenosis that achieve remission have fewer dilations compared with those with ongoing disease activity. Taken together, these data along with the distensibility data suggest that treatment can improve outcomes in patients with inflammatory and fibrostenotic conditions.

Although 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 found that active disease strongly correlates with a worse quality of life.¹⁰ 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 symptoms to maintain enhanced quality of life and improved natural history.^{6–8} Thus, multiple factors, including esophageal endoscopic appearance, histologic findings, 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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