

Eosinophilic esophagitis: Time to classify into endotypes?



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Eosinophilic esophagitis (EoE) is a chronic, primarily food antigen-driven disease with a complex immune-mediated pathophysiology, limited treatment options, and no serum-based biomarker to measure disease activity.¹ EoE disease expression can be heterogeneous, including response to treatment.² Variable EoE clinical phenotypes have been noted, including cases associated with atopy, connective tissue disorders, responsiveness to a proton pump inhibitor, oral immunotherapy (OIT), and early fibrosis.^{2,3} Male predominance is another distinguishing characteristic of EoE for unknown reasons.⁴

Similar to work in other diseases, stratifying patients with EoE by endotype will likely aid in more selective individualized therapy and, ultimately, improved care. Innovative collaborative research that includes large patient cohorts will aid in identifying endotypes for eosinophilic gastrointestinal disorders, such as EoE.⁵

In this issue of the *Journal*, Schuyler et al⁶ present an interesting case for EoE patient stratification based on IgG₄ levels to cow's milk (CM) proteins. To date, clinical and translational studies do not support a prominent role for IgE in patients with EoE.^{7,8} However, high levels of serum and esophageal IgG₄, an immunoglobulin that is thought to be a primary mediator of allergen tolerance, have been associated recently with active EoE disease.^{9,10} In addition to its role in atopic disease, IgG₄ has been described in the pathophysiology of other diseases, such as pemphigoid disease and autoimmune pancreatitis.¹⁰

The mechanism behind IgG₄-related diseases might be due to a prominent cytokine cascade, including IL-10 and TGF- β 1 production, which triggers expansion of IgG₄-producing plasma cells and varying degrees of fibrosis.¹⁰ Similarly, in patients with EoE, it is believed that a local T_H2 response to a food antigen ultimately results in recruitment and activation of the eosinophils and mast cells that secrete a multitude of cytokines, including IL-10 and TGF- β 1, leading to esophageal remodeling and fibrosis. The contribution of IgG₄ to the pathophysiology and natural history of EoE has become a recent focus in EoE research.

Schuyler et al⁶ demonstrated that levels of serum IgG₄ (sIgG₄) specific for CM proteins were greater in patients with active EoE than in subjects in an unselected birth cohort but that these sIgG₄ levels did not reach the markedly increased levels seen in patients with known IgG₄-related diseases. Although sIgG₄ levels to CM proteins were significantly greater in the EoE cohort ($P < .001$), the range of values spanned several logs. This large spread of sIgG₄ values in the EoE cohort, as well as the high sIgG₄ levels to CM detected in control subjects, suggests a low specificity for EoE and little potential for CM-specific IgG₄ levels as a serum-based diagnostic test for EoE. Yet we propose that stratifying patients with EoE based on sIgG₄ levels to CM might provide insight into the local esophageal immune response (eg, high vs low TGF- β 1 levels) and perhaps EoE disease course or treatment response. It has been proposed that the more recently described entity of proton pump inhibitor-responsive EoE lies on the less severe end of the EoE spectrum and the fibrotic phenotype with stricture formation lies on the more severe end associated with a difficult clinical course and often with unresponsiveness to conventional therapies (Fig 1).

We hypothesize that the high-IgG₄ EoE population has stronger association with a more fibrotic clinical phenotype similar to IgG₄-related autoimmune diseases. Thus would the low-IgG₄ EoE population be more likely to respond to proton pump inhibitors? Perhaps sIgG₄ to CM proteins could be used as a prognostic tool to help clinicians to identify patients who might have a more severe and difficult-to-treat form of EoE and therefore to escalate therapy earlier to improve outcomes.

Given the 3-to-1 male predominance seen in patients with EoE,⁴ it is intriguing that the authors show a more robust odds ratio for high-titer sIgG₄ to CM proteins in boys with EoE compared with control subjects. The authors also found a trend toward higher levels of sIgG₄ to CM proteins in boys with EoE than in girls with EoE, but they note that this did not reach statistical significance. The role of sex in the pathogenesis and clinical course of EoE is being investigated, but there is some evidence that female subjects are more likely to complain of atypical symptoms, such as chest pain and heartburn, whereas male subjects are more likely to complain of dysphagia and have a history of food impaction.⁴ If we assume that food impaction and dysphagia are "later" symptoms related to fibrosis, are male subjects more likely to have a fibrotic phenotype? Although it takes many leaps of assumption, we question whether the immune response that results in sIgG₄ to CM having higher titers in male than in female patients with EoE can help explain some of the symptomatic and disease course differences seen clinically.

Measuring disease severity and response to treatment is the ultimate clinical goal. This study only looked at patients with active EoE; however, a small group whose EoE went into remission on CM elimination did not demonstrate changes in sIgG₄ levels that were different than those in subjects with persistently active EoE disease despite CM elimination. Therefore sIgG₄ levels to CM protein likely have poor specificity in predicting EoE trigger foods. However, IgG₄'s relationship to allergen

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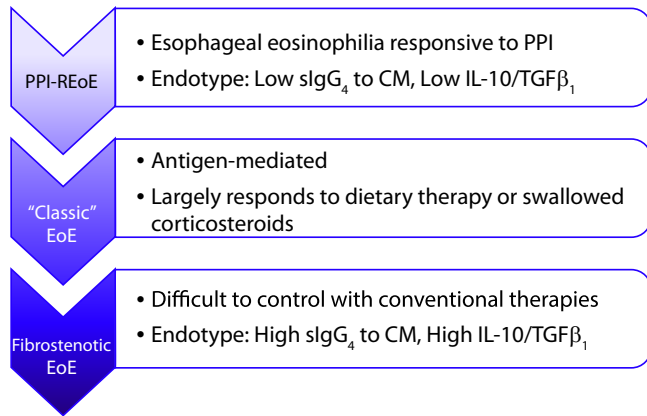


FIG 1. Proposed spectrum of EoE endotypes based on sIgG₄ levels to CM proteins. A proposed EoE disease spectrum that considers treatment response and endotype, including CM-specific IgG₄ levels and possible immunophenotypes, is shown. *PPI*, Proton pump inhibitor; *PPI-REoE*, PPI-responsive EoE.

tolerance raises important questions regarding a small cohort of patients with EoE after OIT.³ Could we use sIgG₄ levels to CM or sIgG₄ CM/IgE ratios during OIT to determine which patients are at higher risk for EoE?

Although sIgG₄ to CM cannot be used as a biomarker of EoE disease activity or response to dietary elimination, this important study raises many new intriguing questions and adds another small piece to the EoE puzzle. sIgG₄ levels to CM appear to identify patients, especially male patients, with active EoE, but whether sIgG₄ is pathogenic or an epiphenomenon of the local immune response remains to be determined. The data presented

also raise hope that stratifying patients into disease endotypes will ultimately help clinicians provide more accurate long-term prognoses and that targeted improved therapies to children with EoE are on the horizon.

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