



Editorial

Challenges with the technical review of eosinophilic esophagitis: discussion points for the practicing allergist



As allergy-immunology coauthors of the *Technical Review on the Management of Eosinophilic Esophagitis (EoE): a report from the American Gastroenterological Association Institute and the Joint Task Force on Allergy-Immunology Practice Parameters*,¹ we wish to raise some fundamental discussion points that could affect the practicing allergist. The guidelines were completed using an iterative process with concerns raised by the working group that were addressed on multiple conference calls and resolved by consensus of the majority and not necessarily by a unanimous decision. Despite this usual consensus-generating paradigm, a few salient points should be discussed further. As practicing allergists involved in the care of patients with EoE, we propose that the following issues merit deeper consideration.

All technical reviews and consensus documents should rely on a standard primary outcome for measuring the efficacy of a medical intervention, the proverbial “gold standard.” To this end, the technical group agreed that the gold standard for the treatment of disease was the resolution and normalization of esophageal biopsies based on eosinophil counts per high powered field, and that resolution of eosinophilia should serve as the primary outcome variable.^{2,3} This goal is similar to that for Crohn’s disease, in which the goal of therapy is the normalization of biopsies and mucosal healing,⁴ or asthma, in which improvement in spirometry is critical.

Disclosures: Dr Spergel reports being a member of the advisory board and receiving honorarium from DBV Technologies; serving as a consultant and receiving fees from DBV Technologies and Regeneron; serving as a speaker and receiving fees from Abbott; and having contracted research and receiving a grant from Novartis. Dr Aceves reports being a coinventor of oral viscous budesonide, with University California San Diego patent and licensed by Takeda; serving as a consultant for Aimmune, AstraZeneca, and Astellas; and receiving funding from National Institute of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Dr Greenhawt reports being an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intrimmune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Sanofi/Genzyme, Genentech, Nutricia, Kaleo Pharmaceutical, Nestle, Aquestive, Allergy Therapeutics, AllerGenis, Aravax, GlaxoSmithKline, Prota, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received an honorarium for lectures from Thermo Fisher, Aimmune, DBV, Before Brands, multiple state allergy societies, the American College of Allergy Asthma and Immunology, and the European Academy of Allergy and Clinical Immunology; is an associate editor for the *Annals of Allergy, Asthma & Immunology*; and is a member of the Joint Task Force on Allergy Practice Parameters.

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However, for dilation studies and studies using montelukast, the primary outcome was changed to symptoms rather than eosinophilia. This occurred despite the agreement that distinct primary outcome variables could not be fairly compared with treatment strategies. In this context, it is important to make 2 observations: (1) patients with EoE can have an active disease but remain minimally symptomatic or asymptomatic owing to acclimation (if these are long-standing) or compensatory eating methods to defray the sensation of dysphagia; and (2) the interpretation of montelukast or dilation using the end point of histologic eosinophil improvement would have rendered both of these interventions as ineffective and not recommended. Although critical strictures absolutely require esophageal dilation, it is essential to note that stricture and food impaction recurrence is likely without concomitant anti-inflammatory or antieosinophil therapy.⁵ As such, we would contend that montelukast has no role in EoE therapy and that dilation should be a therapy with concurrent anti-inflammatory regimen rather than considered an appropriate isolated therapy. Therefore, we contend that it remains unclear why these 2 therapies were included in light of symptom relief being a very different outcome.

Another issue is that of elimination diet, which has appeared repeatedly in the literature as an effective intervention in EoE but universally downgraded. This is due to the foundation of Grading of Recommendations, Assessment, Development and Evaluations (GRADE) recommendations, which requires a placebo control arm for a study to be considered to be of the highest quality. However, owing to the multiple food avoidances implemented in EoE, the use of a placebo control group is virtually impossible. Although the use of placebo in future single-food elimination trials (eg, milk elimination only) may be feasible, we would contend that food elimination is a proven effective therapy for EoE that does not necessarily warrant downgrading in the absence of a placebo arm. We acknowledge that the GRADE recommendations for these diet strategies do appropriately consider single-arm observational studies and large case series as imprecise, indirect, and suffering from selection bias when rating the certainty of pooled evidence. However, the methodology team chose to enact an allowable (but potentially confusing) convention of using a historical placebo group pooled from the steroid analyses to serve as a surrogate control arm. This surrogate arm relies on the presumption that persons randomized to placebo in studies are not expected to show therapeutic improvement and that a historical group could therefore serve as a control group in this setting, with additional downgrading being accounted for in the process. Although the theory herein may make sense, it leaves several questions with unsatisfactory answers including (1) whether steroid arm placebo

Table 1
Summary of Effectiveness of EoE Therapies

Therapy	Relative risk for histologic remission of EoE (95% CI)	Ability for normalization of histology	Practical considerations
Elemental diet	0.07 (0.05–0.12)	93%	Inconsistent coverage by insurance, poor adherence, multiple endoscopies
Six-food group elimination diet	0.38 (0.32–0.43)	62%	Poor adherence, multiple endoscopies
Topical corticosteroids	0.39 (0.26–0.58)	61%	Inconsistent coverage by insurance, candida
Four-food group elimination diet	0.49 (0.42–0.57)	51%	Poor adherence, multiple endoscopies
Single-food elimination diet	0.52 (0.37–0.74)	48%	Variable efficacy
Allergy testing elimination diet	0.57 (0.33–0.73)	43%	Multiple endoscopies
Two-food group elimination diet	0.66 (0.57–0.77)	34%	Variable efficacy
PPI	0.66 (0.61–0.72)	34%	Variable efficacy
Cromolyn	0.89 (0.71–1.12)	21%	Lack of efficacy
Anti-IL5	0.92 (0.84–1.00)	8%	Lack of efficacy
Anti-IL13	0.94 (0.67–1.30)	6%	Lack of efficacy
Esophageal dilation, montelukast	No data	—	Lack of efficacy on histology

Abbreviations: CI, confidence interval; EoE, eosinophilic esophagitis; PPI, proton pump inhibitor; RR, relative risk.

groups truly have no therapeutic response given the potentially waxing and waning nature of EoE because of aeroallergen exposures, (2) whether the population of patients who would enter a randomized elimination diet trial is the same clinically as those in a steroid trial, and (3) whether a placebo arm would truly affect the point estimates for the efficacy of elimination diets. In addition, we would contend that more thought should have been given to the pooling of multiple elimination diet studies because not all empiric elimination diets were identical in their eliminated foods, which in turn could lead to differences in patient adherence. Despite the downgrading, both elemental and empiric diet show very strong efficacy rates notwithstanding the low certainty of evidence (Table 1).

Another point of contention was the manner in which studies that used allergy testing were analyzed. For recommendations on diet directed by food allergy testing, skin prick testing and specific IgE and atopy patch testing were grouped as equal modalities and into 1 composite measure irrespective of which test or tests were used in a study, making it impossible to understand if there is a difference in outcome based on testing method. An allergist-immunologist knows that skin testing is not necessarily equivalent to specific IgE testing, and because these tests have different properties, this should have been analyzed individually to give the most unbiased assessment. This is important in light of mounting evidence demonstrating that EoE is not primarily an IgE-mediated driven disease and because IgE allergy tests would potentially represent the wrong instrument for the measurement of potential food triggers. We would contend that this should have been given deeper consideration in the analysis.

Finally, with regard to the elimination diet, we posit a further consideration of unequal weighting in the analysis. The rationale behind why elemental diet and empiric diet were rated with slightly higher certainty compared with a testing-directed diet remains unclear and unsettled among the allergy workgroup. Although the reason stated was the width of the confidence intervals, given the lack of a placebo group in any of the elimination diet trials, it stands to reason that all 3 diets should have had an equal “low certainty” rating. By using an equal certainty rating between the diets, one can appropriately conclude that there should not be a presumption of any hierarchy in the choice of a dietary approach. We further acknowledge that utilization of a testing-based diet in adults has little success, which may be different from what is seen in children, but this was not accounted for in the guidelines.

In terms of the topical corticosteroid recommendations, an astute reader will quickly note that this recommendation actually

has the highest certainty of evidence of any strategy and the strongest recommendation. The decision was made to group all topical corticosteroids into 1 analysis makes sense in terms of numbers; but it does not account for important differences that could bias outcomes such as dose, distribution of the vehicle in a slurry vs a propellant, and steroid potency.

In addition, there is little discussion regarding the balance between a requirement for placebo-controlled data and the practical ability of being able to complete such a trial. In the case of allergy immunotherapy, it will be very difficult to clarify its role in the management of EoE. We propose that current data support immunotherapy as a useful adjuvant treatment in EoE.

Perhaps the most salient to the practicing allergist is how to implement the data provided in the guidelines. We wish to provide some clarity on how to rank the interventions. To do this, we have reconstructed a chart ranking the relative risk reduction from these therapies (Table 1), as opposed to the current guideline document in which the convention of reporting is reversed and denotes the risk that a patient will NOT improve on therapy. For example, in the current guidelines, a relative risk of 0.07 means that 93% of the patients will have resolution of their eosinophil counts (ie, a good response), and relative risk of 0.92 means only 8% of the patients will have resolution of their counts (ie, a poor response). Using this more standard description of the outcome, the elemental diet has the best risk reduction. The next best outcome would be a 6-food elimination diet followed by topical corticosteroids. As with any recommendation, choice of therapy has to be tempered with the practicality of the intervention. Although very effective, the elemental formula is not a good choice in terms of lifestyle for most patients. In contrast, topical corticosteroids are easier to use and maybe more appealing, thereby leading to increased adherence to a recommended therapy. There are new biologicals that look promising; dupilumab in the phase 2 study had 78% normalization of histology.⁶

We acknowledge that no GRADE analysis or systematic review will ever be perfect. The American Gastroenterological Association and Joint Task Force of the Allergy-Immunology Practice Parameters on EoE Guidelines and Technical Report do represent the latest in terms of high-level, evidence-based guidelines using GRADE, and are a major step forward for 2 specialties to jointly produce a set of recommendations for the care of a shared disease. However, our point is to highlight that although this review was well done, it has controversies and some pending issues that merit deeper discussion. This is not unique, but in the case of a combined specialty guideline, these discussion points may be magnified. The final decision is a shared decision between the

patient and provider, and more studies comparing treatment modalities are needed.

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