



Targeting and Manipulating Type 2 Inflammation in Eosinophilic Esophagitis

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Conflicts of Interest

- None to disclose

Objectives

- 1) Review our historical understanding of eosinophilic esophagitis (EoE) pathophysiology
- 2) Understand eosinophilic esophagitis (EoE) as a disease of type 2 (T2) inflammation, and approaches to interrupt T2 inflammation
- 3) Appreciate the value of a multi-disciplinary team in EoE management
 - manipulating T2 inflammation
 - managing clinical and psychosocial consequences

Objective 1

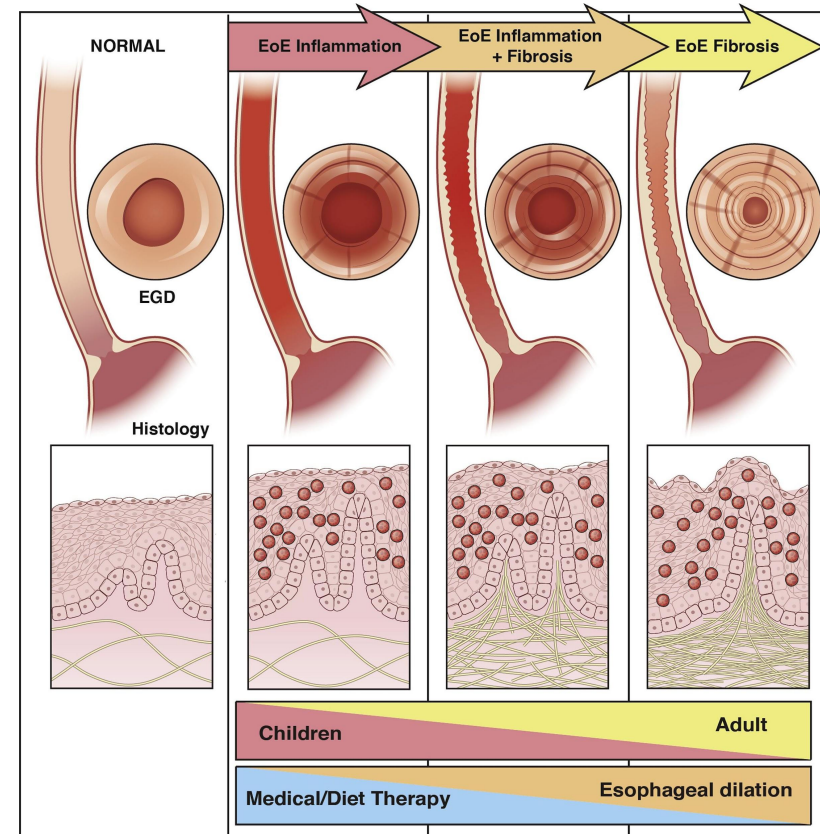
Review our historical understanding of eosinophilic esophagitis (EoE) pathophysiology



Eosinophilic Esophagitis is a chronic, antigen-mediated disorder...

...defined by a combination of

- Clinical symptoms and consequences of esophageal dysfunction
- Endoscopic findings that are distinct
- Histopathological findings
 - Elevated eosinophils (>15/hpf)
 - Epithelial proliferative changes



Dellon and Hirano. Gastro. 2018.

EoE: A History

1990s: Incidence of EoE in Hamilton County, Ohio. Eos and atopy.

Eosinophilic Esophagitis

TO THE EDITOR: Eosinophilic esophagitis is an emerging disease worldwide, as documented by recent case series from Switzerland, Australia, Italy, Spain, Japan, England, and the United States.¹⁻³ Eosinophilic esophagitis mimics gastroesophageal reflux disease and may result in narrowing and stricture of the esophagus.¹⁻³ This disease is differentiated from reflux esophagitis on the basis of the magnitude of mucosal eosinophilia and a lack of response to acid suppression.⁴ We report findings from a population-based demographic study of the pediatric population with eosinophilic esophagitis residing in the vicinity of our medical center (Hamilton County, Ohio), a region with a single pediatric gastroenterology and pathology provider.

Cases of eosinophilic esophagitis were systematically identified from our institution's pathology database; the criteria were the presence of epithelial proliferative changes (e.g., thickening of the basal epithelial layer and elongation of the papillae), a minimum of 24 eosinophils per high-power field ($\times 400$) in the distal esophagus, and the ab-

sence of eosinophilia in any other intestinal segment. Data from the 2000 Census for the population 0 to 19 years of age were used to calculate frequency.

During the years 1991 through 2003, there were 924 possible cases of eosinophilic esophagitis, of which 315 were subsequently found to meet the diagnostic criteria. Of the 315 cases, only 2.8 percent had been identified before 2000. A total of 103 patients with conditions that met the histologic criteria for the disease resided within Hamilton County at the time of diagnosis. More than 70 percent of these 103 patients had coexisting eosinophilic involvement in the proximal esophagus. Approximately 71 percent were male, with a mean (\pm SD) age of 10.5 \pm 5.4 years. The patients presented with the typical symptoms and atopic history that have been described previously (Tables 1 and 2).¹⁻⁴ However, our demographic analysis revealed a strong familial pattern (Table 2), including three sibling pairs; the mother of one of the pairs of siblings was also given a diagnosis of eosinophilic esophagitis at our institution. The familial cases of eosinophilic

Early 2000s: Food antigens trigger and maintain EoE

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Elemental Diet Is an Effective Treatment for Eosinophilic Esophagitis in Children and Adolescents

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OBJECTIVE: Eosinophilic esophagitis (EoE), a disorder characterized by eosinophilic infiltration of the esophageal mucosa, has been defined in large part through published case reports and series leading to ambiguity in both diagnostic and treatment options. Corticosteroids, cromolyn, and elemental diet have all been reported as successful treatments for EoE. In this study, we sought to accurately define a population of patients with EoE and then assess their response to elemental diet.

METHODS: A series of patients with chronic symptoms of gastroesophageal reflux disease and an isolated esophageal eosinophilia on esophagogastroduodenoscopy (EGD) were identified. Therapy with a proton pump inhibitor was instituted for 3 months, followed by repeat EGD when symptoms persisted. A 24-h pH probe study was performed, and those with significantly abnormal studies were excluded. The remaining patients were diagnosed with EoE and placed on an elemental diet for 1 month, followed by a repeat EGD.

RESULTS: Of 346 patients with chronic gastroesophageal reflux disease symptoms and eosinophils on esophageal biopsy, 51 (14.7%) were ultimately diagnosed with EoE. There was significant improvement in vomiting, abdominal pain, and dysphagia after the elemental diet. The median number of esophageal eosinophils per high-powered field (HPF) decreased from 33.7 before the diet to 1.0 after the diet ($p < 0.01$). The average time to clinical improvement was 8.5 days.

CONCLUSIONS: Elemental diet resulted in striking improvement in both symptoms and histologic evidence of disease in children and adolescents with EoE, as identified by strict diagnostic criteria. (Am J Gastroenterol 2003;98:777-782. © 2003 by Am. Coll. of Gastroenterology)

esophageal reflux disease (GERD) and include vomiting, regurgitation, nausea, epigastric pain, heartburn, and dysphagia. In both groups, the symptoms typically improve with acid blockade; however, whereas patients with GERD generally become symptom free and demonstrate a resolution in their esophagitis, children with EoE almost always continue to exhibit clinical symptoms and display no histologic improvement despite aggressive acid blockade.

The spectrum of EoE has been described predominantly by case reports and case series. However, in the majority of these reports, there has been considerable variability in the criteria used to define EoE. Although effective treatment regimens for EoE have also been reported, these series are also limited by a lack of consistent outcome measures.

The aims of this study were to accurately define a population of patients with EoE, to study the effect of aggressive acid blockade on EoE, and to evaluate the treatment of EoE patients with dietary restriction using a complete elemental diet.

MATERIALS AND METHODS

This study was conducted from January 1, 1997, to January 1, 2000, in the Division of Gastroenterology and Nutrition at the Children's Hospital of Philadelphia. Patients were initially identified if they had chronic GERD symptoms (3 months or more), normal upper GI anatomy based on barium upper GI series, and evidence of an isolated esophageal eosinophilia by esophagogastroduodenoscopy (EGD) with biopsy. GERD symptoms included vomiting/regurgitation, epigastric pain, or at least two of the following: heartburn, water brash, globus, chest pain, dysphagia, nighttime cough, feeding disorder, or irritability. Symptoms were assessed by

Current understanding: EoE as "Type 2" Esophagus

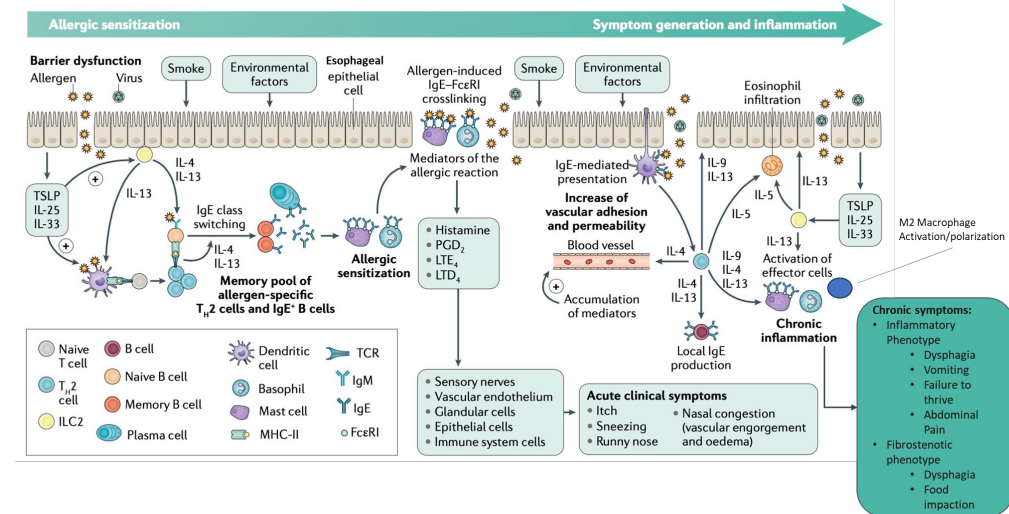


Table 1. Presenting Symptoms among 103 Pediatric Patients with Eosinophilic Esophagitis.*

Symptom	Median Age (Interquartile Range)	No. (%)
Feeding disorder	2.0 (1.2-6.2)	14 (13.6)
Vomiting	8.1 (3.5-12.3)	27 (26.2)
Abdominal pain	12.0 (9.6-15.2)	27 (26.2)
Dysphagia	13.4 (10.0-16.7)	28 (27.2)
Food impaction	16.8 (13.7-19.6)	7 (6.8)

* Patients may have had more than one symptom, but only the most prominent symptom is included here. The median age varied significantly according to the primary symptom ($P < 0.001$) by the Kruskal-Wallis test.

Table 2. History of Atopy in the 103 Pediatric Patients.

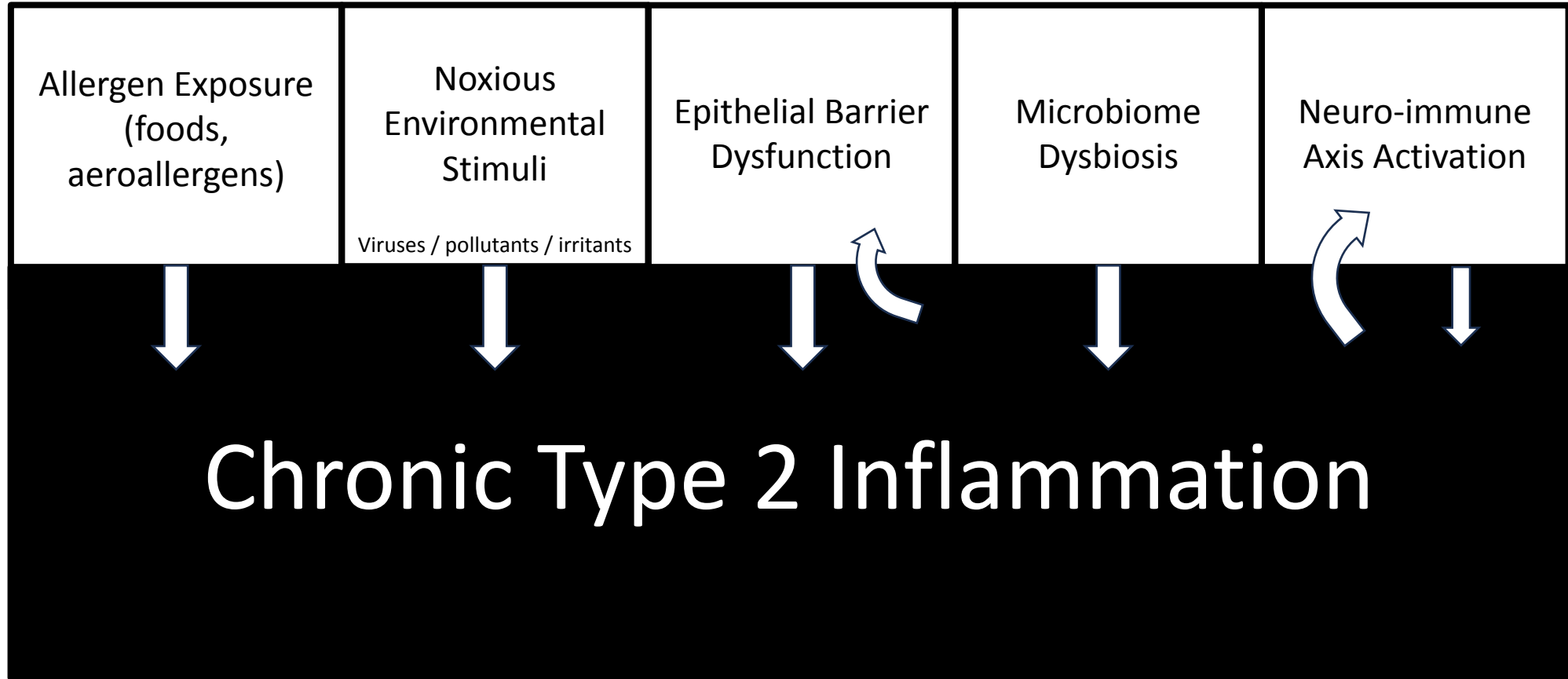
Variable	Percent of Patients
Rhinoconjunctivitis	57.4
Wheezing	36.8
Possible food allergy*	46
Family history of atopic disease	73.5
Family history of eosinophilic esophagitis†	6.8
Family history of esophageal dilatation	9.7

* There was a history of a positive response to skin-prick test or to a radioallergen sorbent test, or an anaphylactic response to a specific dietary antigen.

† The diagnosis of eosinophilic esophagitis was made at our institution for patients with a family history of the disease (i.e., in a first-degree relative).

Objective 2

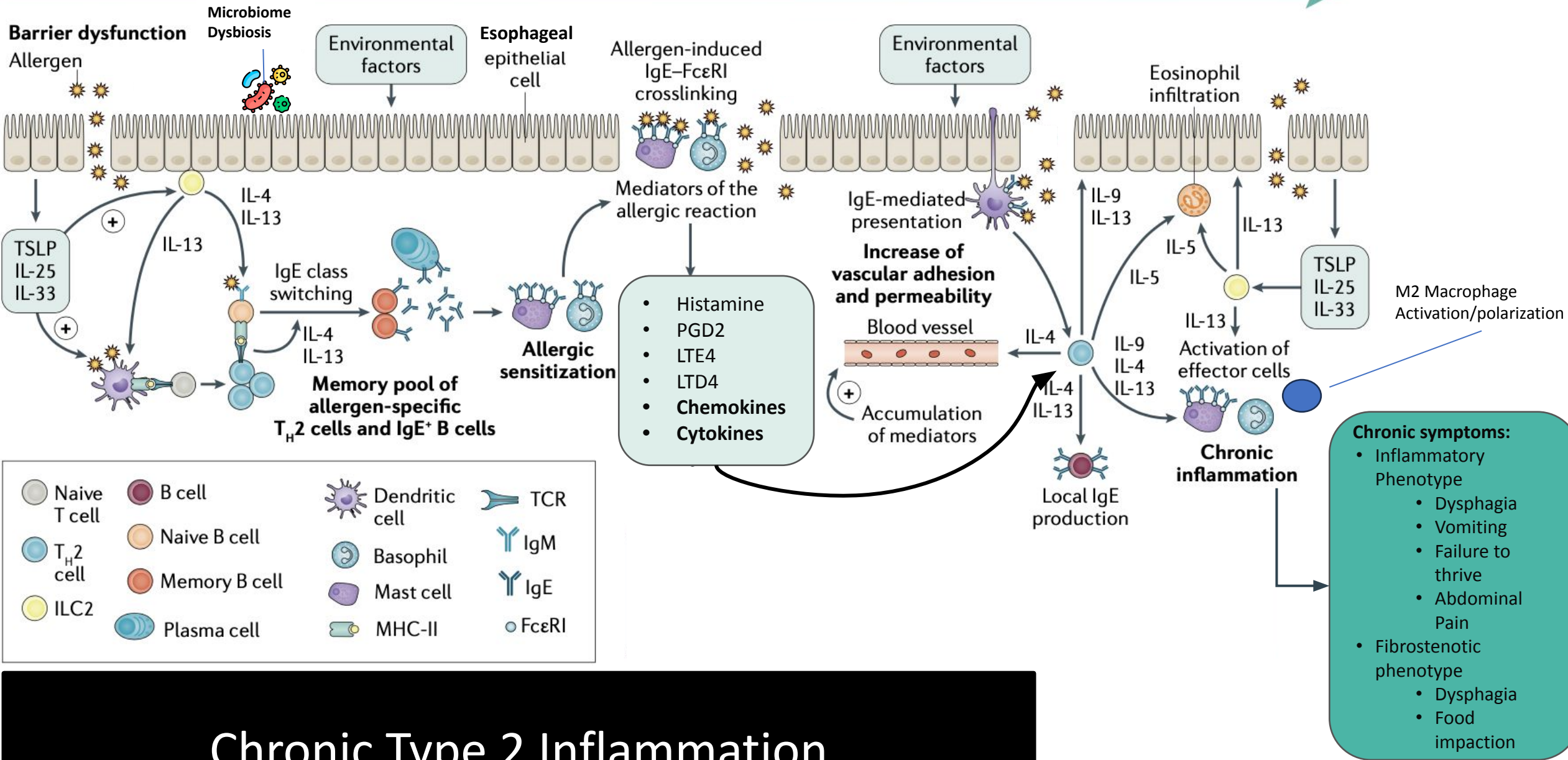
Understand eosinophilic esophagitis (EoE) as a disease of type 2 (T2) inflammation, and approaches to interrupt T2 inflammation



in an individual who is atopic –
the genetic predisposition to having type 2 inflammation

Allergic sensitization

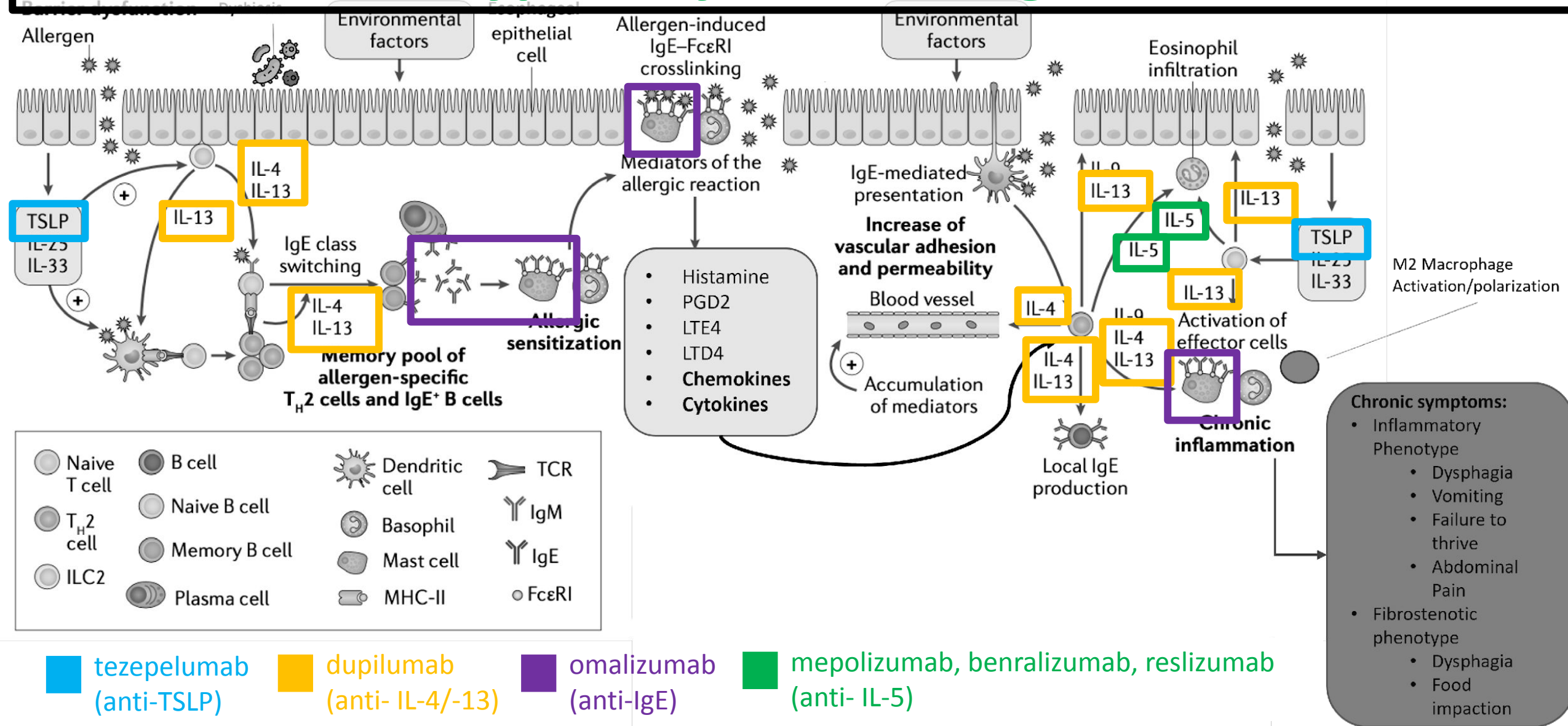
Symptom generation and inflammation



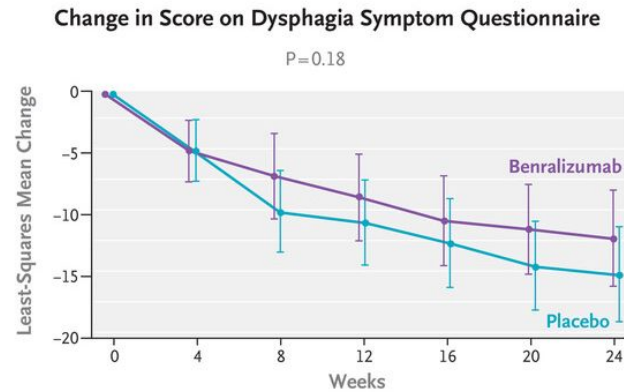
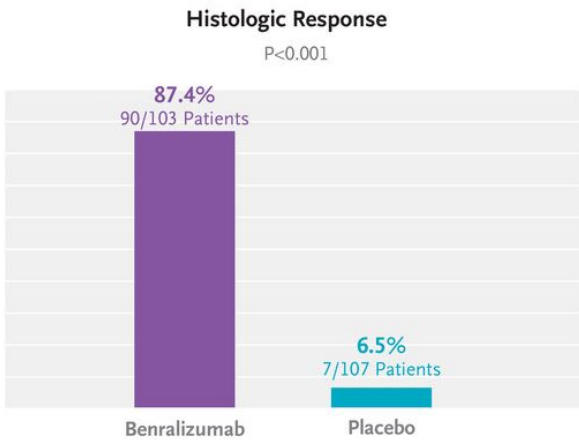
Chronic Type 2 Inflammation

Modified from Bousquet et al. Nature Reviews Disease Primers. 2020.

Type 2 cytokine targets



Anti-IL-5 agents target eosinophils and induce histologic remission, but **not clinical remission** in adults with EoE

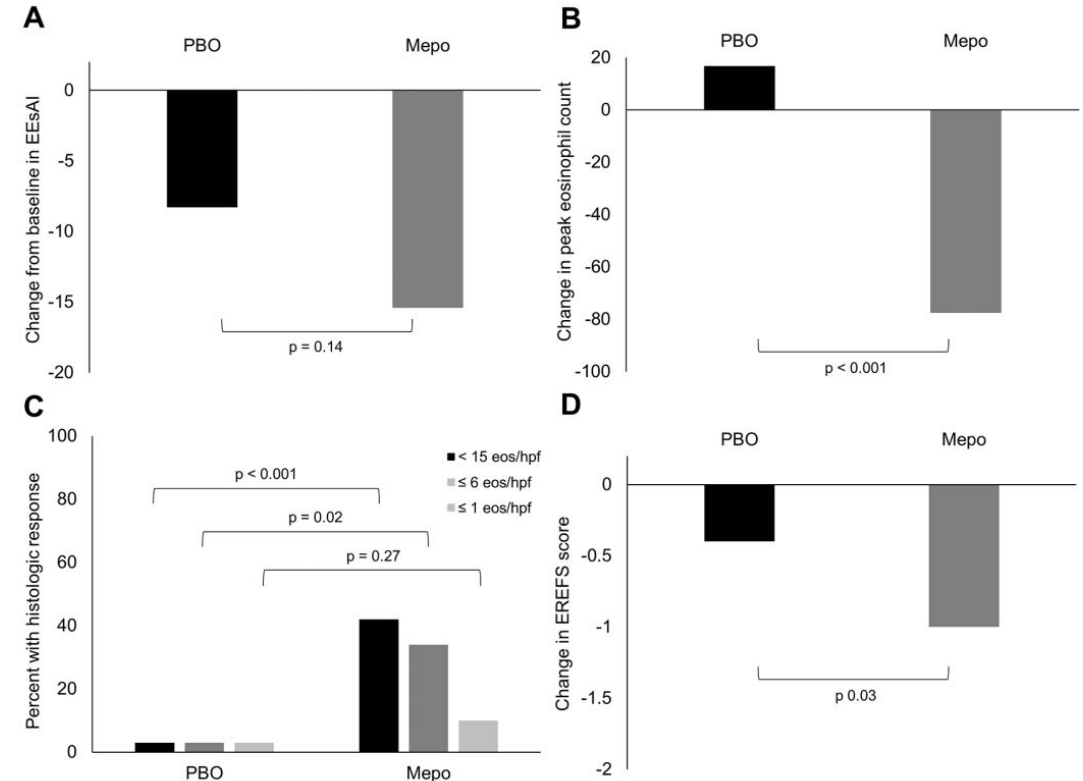


HISTOLOGY AND SYMPTOMS

Benralizumab reduced eosinophil counts but had no effect on dysphagia symptoms.

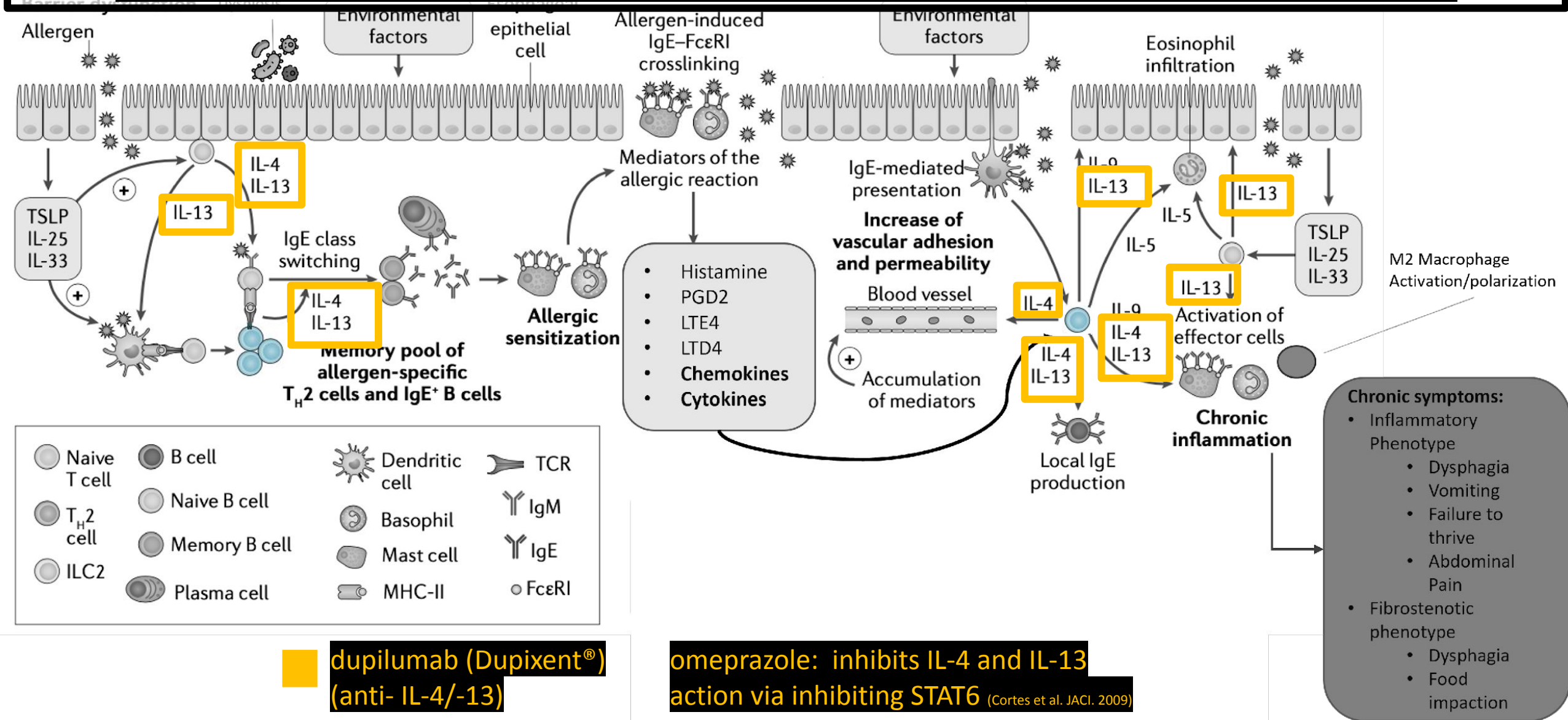


MESSINA trial (Benralizumab for EoE)
Rothenberg et al. NEJM. 2024.

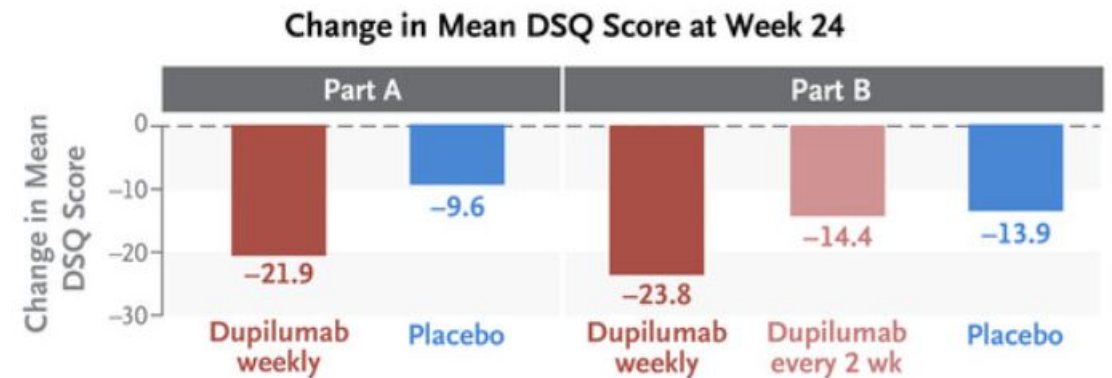
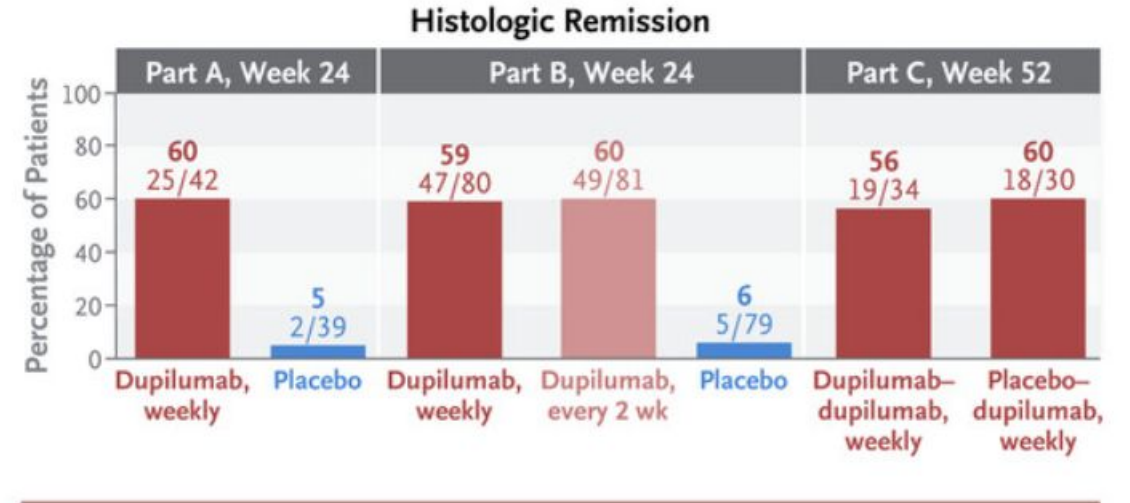
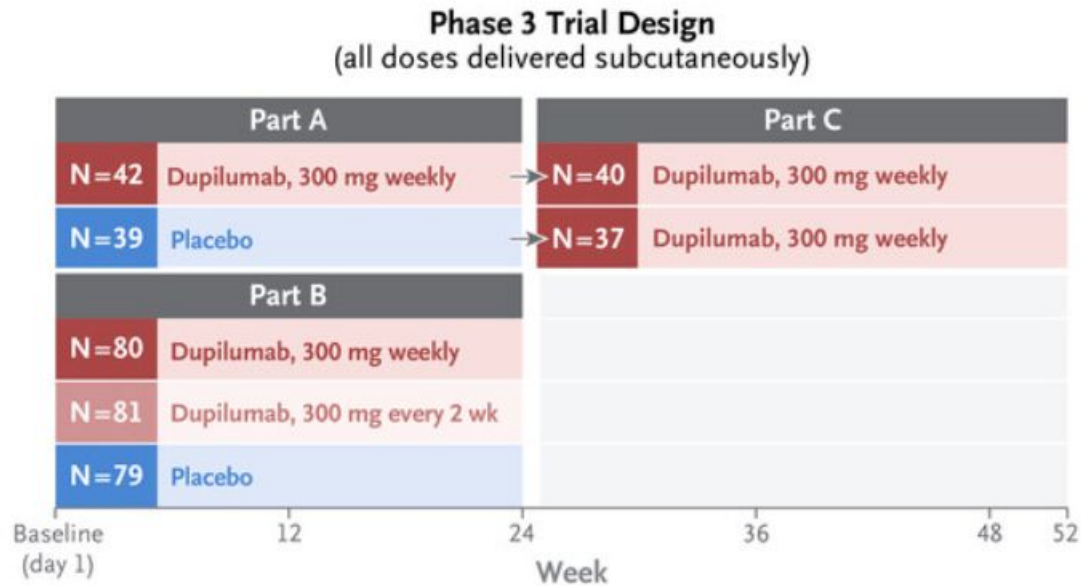


Mepolizumab for EoE trial
Dellon et al. Gut. 2023.

IL-4 and IL-13 are important Type 2 cytokines



Dupilumab (Dupixent®) targets type 2 cytokines, induces and maintains **clinical and histologic remission** in adults with EoE



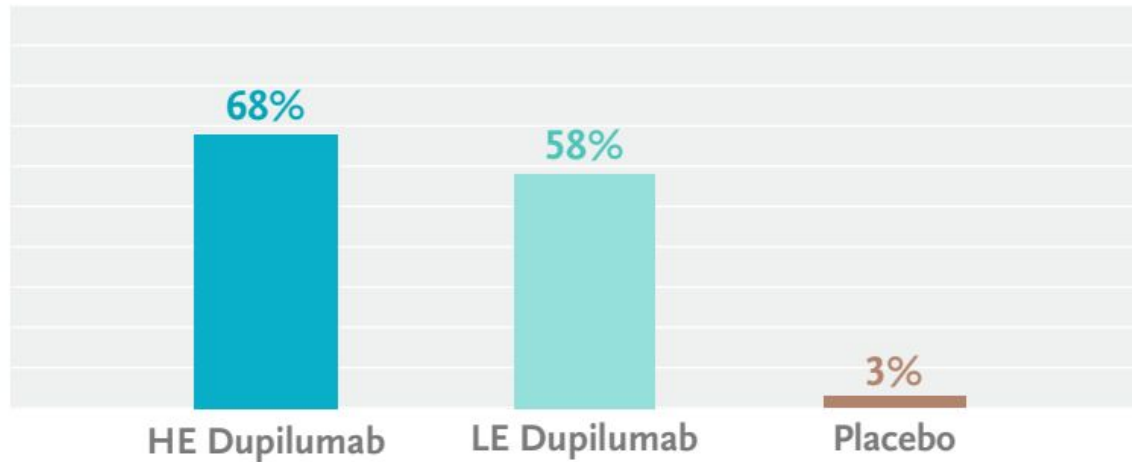
- Adults and adolescents ≥ 12 years of age
- ≥ 15 eos/hpf in esophagus, despite high-dose PPI for 8 weeks

Dellon et al. NEJM. 2022.

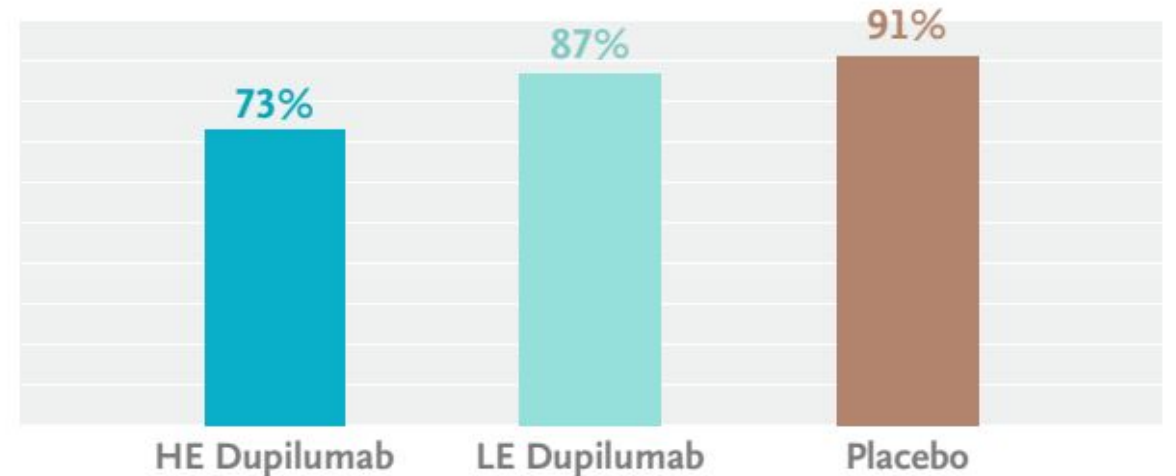
Dupilumab targets type 2 cytokines, induces and maintains clinical and histologic remission in children with EoE

Histologic Remission

P<0.001 for the difference between each dupilumab group and placebo



Any Adverse Event during Part A



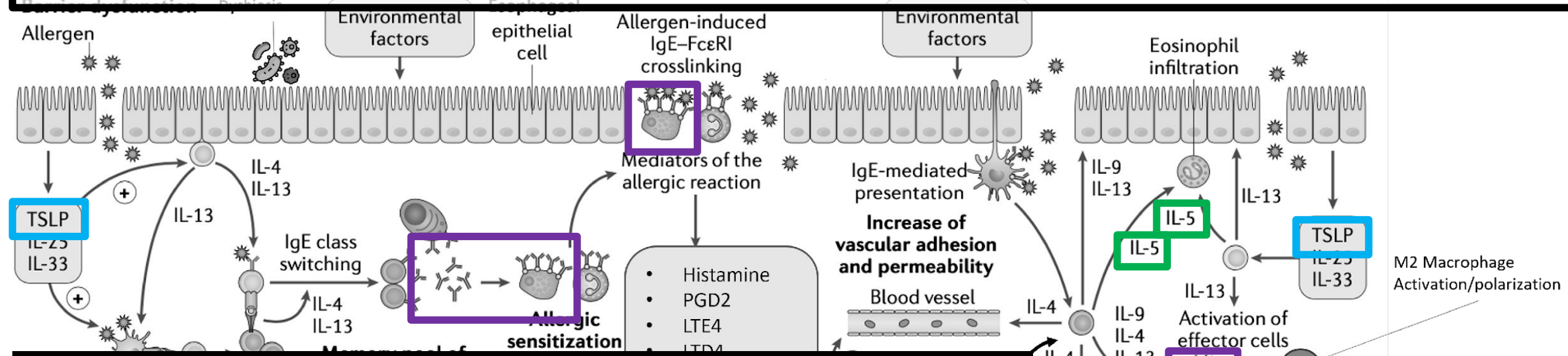
Improvement in all outcomes

- Primary: histologic
- Secondary: endoscopic, transcriptomic

All serious adverse events assessed by investigator to be unrelated to dupilumab

EoE Kids Trial
Chehade et al. NEJM. 2024.

Other type 2 cytokine targets (select list)



Agent	Target	Status
tezepelumab (Tezpire®)	TSLP	Phase 3 trial ongoing (CROSSING trial)
omalizumab (Xolair®)	IgE	lack of efficacy in Phase 2
CC-93538 (aka cendakimab)	IL-13	Phase 3 trial ongoing, efficacy transcriptomic outcomes (Phase 2)
lirentelumab	Siglec-8 (eosinophil)	No change in symptom scores (phase 2/3)

- Chronic symptoms:**
- Inflammatory Phenotype
 - Dysphagia
 - Vomiting
 - Failure to thrive
 - Abdominal Pain
 - Fibrostenotic phenotype
 - Dysphagia
 - Food impaction

Modified from Bousquet et al. Nature Reviews Disease Primers. 2020.

Nhu and Aceves. Annals of AAI. 2023.

2025 American College of Gastroenterology Guideline on the Diagnosis and Management of Eosinophilic Esophagitis (EoE)

Table 1. EoE recommendations

Statement	Quality of evidence	Strength of recommendation
Treatment		
<i>PPIs</i>		
5. We suggest PPIs as a treatment for EoE	Low	Conditional
<i>Topical steroids</i>		
6. We recommend the use of swallowed topical steroids as a treatment for EoE	Moderate	Strong
7. We suggest the use of either fluticasone propionate or budesonide in patients with EoE being treated with topical steroids	Low	Conditional
<i>Biologics</i>		
8. We suggest at least 8 weeks of PPI therapy before considering biologics		
10. We suggest dupilumab as a treatment for EoE in individuals 12 years of age or older who are nonresponsive to PPI therapy	Moderate	Conditional
9. We do not suggest dupilumab as a treatment for EoE in pediatric patients (ages 1–11 years) who are nonresponsive to PPI therapy	Low	Conditional
<i>Biologics</i>		
10. We suggest against using cendakimab, benralizumab, lirentelimab, mepolizumab, or reslizumab as a treatment for EoE	—	—
11. We suggest against using omalizumab as a treatment for EoE	Low	Conditional
<i>Small molecules</i>		
12. We cannot make a recommendation for or against the use of cromolyn and montelukast as a treatment for EoE	Very low	Conditional
13. We suggest against using omalizumab as a treatment for EoE	Low	Conditional
<i>Small molecules</i>		
14. We suggest against the use of cromolyn and montelukast as a treatment for EoE	Very low	Conditional

Aeroallergen Immunotherapy: Use in EoE with aeroallergen sensitization and rhinitis, asthma, and/or atopic dermatitis

Clinical Communications

Complete remission of eosinophilic esophagitis with multi-aeroallergen subcutaneous immunotherapy: A case report



Edward G.A. Iglesia, MD, MPH^a,
Scott P. Commins, MD, PhD^b, and
Evan S. Dellon, MD, MPH^c

Clinical Implications

- Multiallergen subcutaneous immunotherapy might be a safe and effective option for patients with eosinophilic esophagitis and comorbid allergic rhinitis and/or asthma who do not respond to standard therapies, although future controlled studies are needed.

TABLE I. Treatment course

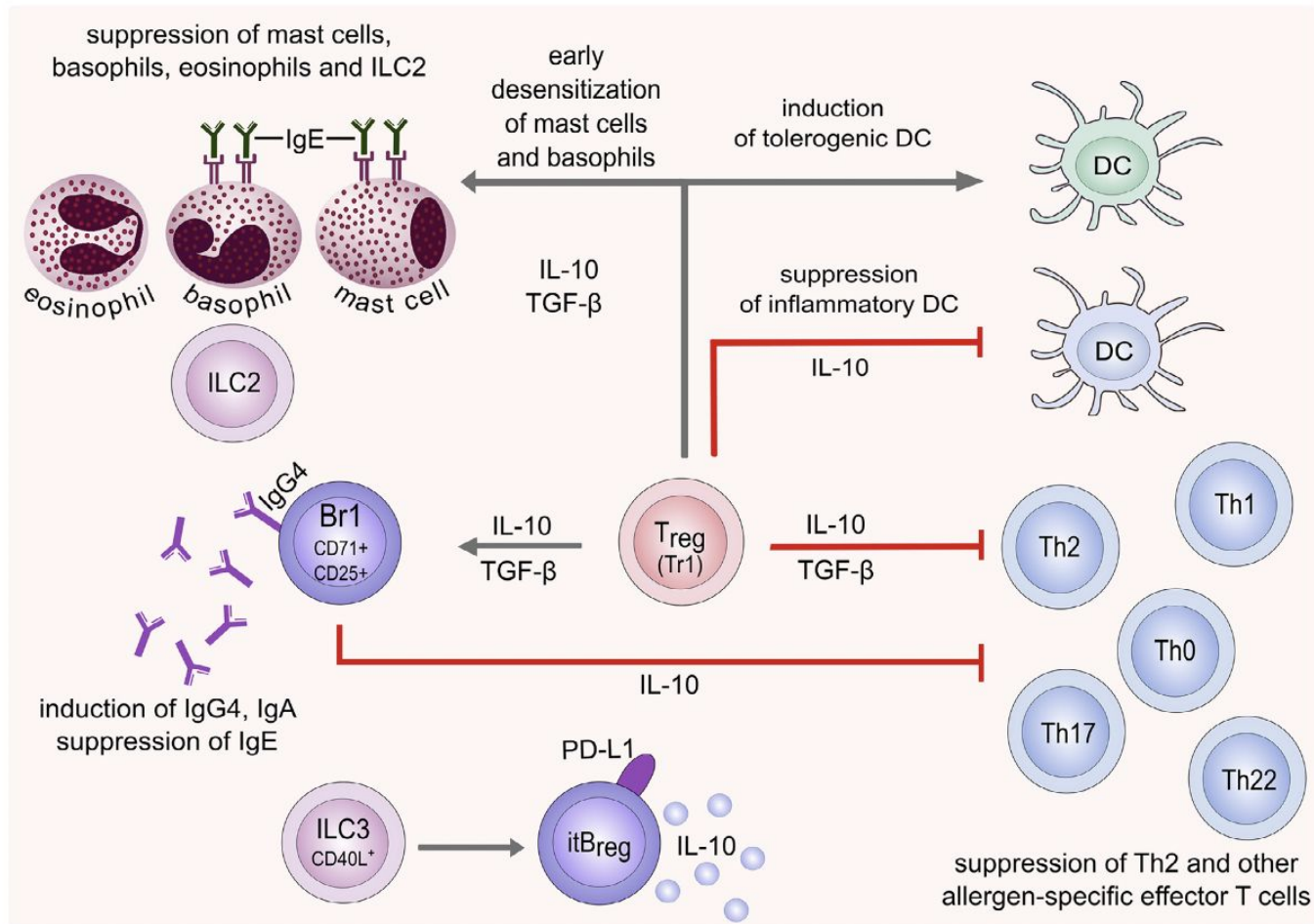
Treatment	Symptom response	EGD outcome (EREFS)	Eosinophil counts, proximal (eos/hpf)	Eosinophil counts, distal (eos/hpf)	Month of biopsy	Additional notes
Omeprazole 20 mg twice daily x 12 wk	No	Ex2, R1, E1, F1, S0 No dilation	62	21	March	
2FED (dairy, wheat) x 8 wk	No	Ex1, R2, E2, F1, S11 No dilation	90	45	August	
4FED (dairy, wheat, egg, soy) x 6 wk	No	Ex1, R2, E1, F1, S9 Dilation (Savary to 11 mm)	180	10	October	
6FED (dairy, wheat, egg, soy, peanuts/tree nuts, fish/shellfish) x 6 wk	No	Ex1, R2, E1, F1, S9 Dilation (Savary to 12 mm)	140	60	November	
OVB 1 mg twice daily x 8 wk	Yes	Ex0, R1, E0, F0, S16 Dilation (Savary to 17 mm)	0	0	March	OVB subsequently stopped owing to family preference to start SCIT and observe response
Off OVB and on multiallergen SCIT (build-up phase) x 3 mo	Yes	Ex1, R1, E1, F1, S16 Dilation (Savary to 17 mm)	0	48	August	
Multiallergen SCIT (maintenance phase) x 3 mo	Yes	Ex1, R0, E0, F1, S0	0	5	March	
Multiallergen SCIT (maintenance phase) x 8 mo	Yes	Ex0, R0, E0, F0, S0	0	2	August	Remains asymptomatic with ≥18 mo of maintenance SCIT; follow-up EGD deferred owing to COVID-19 pandemic

EGD, esophagoduodenoscopy; EREFS, eosinophilic esophagitis endoscopic reference score; eos/hpf, eosinophils per high-power field; FED, food elimination diet; OVB, oral viscous budesonide; Savary, wire-guided bougie type dilator; SCIT, subcutaneous immunotherapy.

Iglesia, Commins, Dellon. JACI-IP. 2021.

Microbiome

A. Głobińska et al. / Ann Allergy Asthma Immunol 121 (2018) 306–312



How does immunotherapy work?

T cells

Upregulation of regulatory T cells (Tregs)

□ Inhibit Th2 axis

B cells

Production of competitive antibodies □

desensitize effector cells

Upregulation of regulatory B cells (Bregs)

Effector cells

Suppression of effector cells

Aeroallergen – subcutaneous immunotherapy

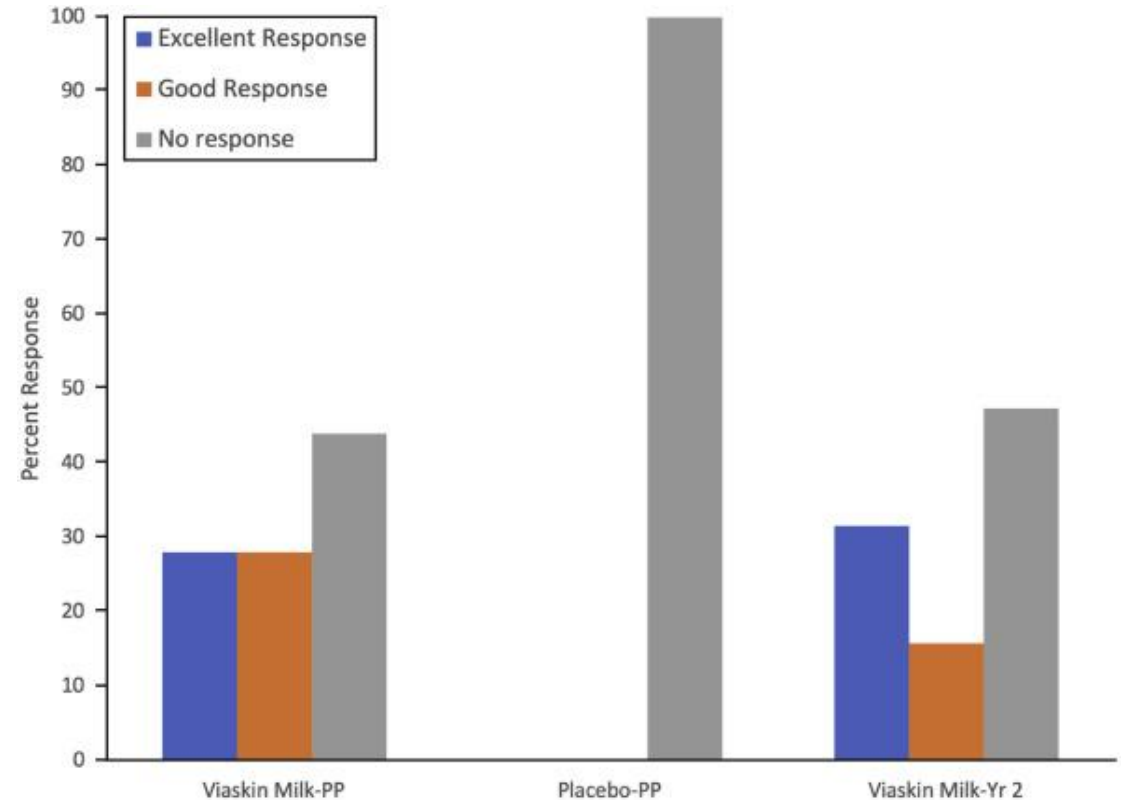
Food – oral immunotherapy

Allergen-Specific Immunotherapy: Chronic High Dose Allergen Exposure Upregulates Tolerogenic Mechanisms (Regulatory T and B Cells)

- Dysphagia
- Food impaction

Investigational: Milk Epicutaneous Immunotherapy (EPIT) for EoE

- Phase 2a (SMILEE study)
- 20 children and adolescents (age 4 – 17 years)
- ITT analysis at 11 months: no significant difference between milk EPIT and placebo
- Open label extension at 2 years: 47% histologic response



Objective 3

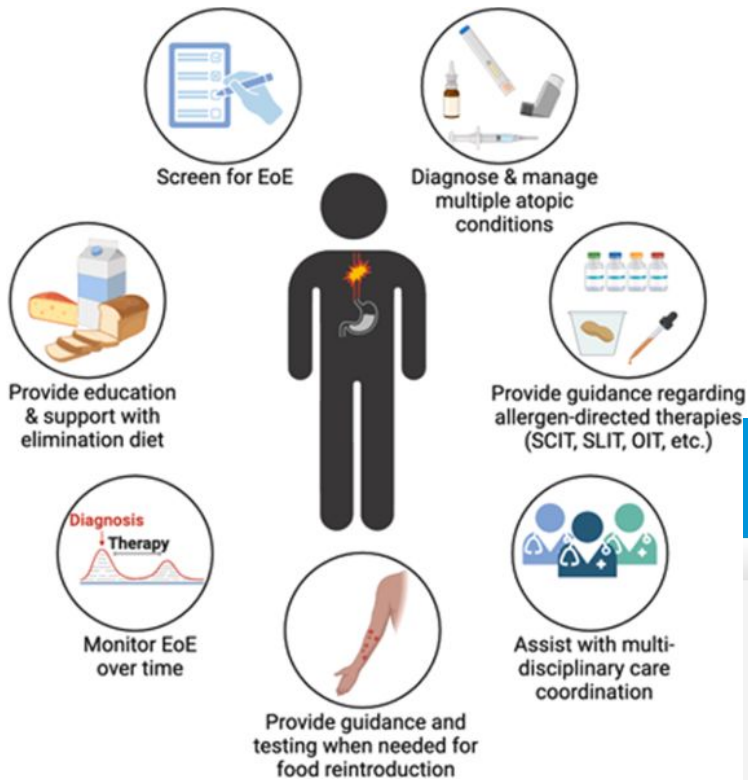
Consider the role of allergen immunotherapy in EoE



The EoE World Needs a Multi-Disciplinary Approach

Identify Clinical Symptoms	<ul style="list-style-type: none">• Gastroenterology• Allergy• ENT, Pulmonology• Speech Language Pathology
Identify, Characterize, and Interrupt/Manage Type 2 Inflammation	<ul style="list-style-type: none">• Gastroenterology• Pathology• Allergy• Nutrition
Manage clinical symptoms and consequences	<ul style="list-style-type: none">• Gastroenterology• Nutrition• Speech Language Pathology• Radiology• Nursing• Psychology
Manage psychosocial consequences	

The EoE World Needs a Multi-Disciplinary Approach



McGowan et al. JACI. 2025.



Clinical and Translational GASTROENTEROLOGY

► Clin Transl Gastroenterol. 2024 Jan 11;15(3):e00672. doi: [10.14309/ctg.0000000000000672](https://doi.org/10.14309/ctg.0000000000000672)

Sleep, Anxiety, Somatization, Quality of Life, and Resilience in Pediatric Patients With Eosinophilic Esophagitis

[Elizabeth T Jensen](#)^{1,✉}, [Kira Chaiboonma](#)², [Oscar Ayala](#)², [Anthony Proia](#)², [Seema S Aceves](#)^{2,3,✉}

Apfed
American Partnership for Eosinophilic Disorders

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Eosinophilic esophagitis (EoE) is a chronic, progressive disease of the esophagus driven by Type 2 inflammation (T2). For many, it causes persistent and life-altering symptoms—and if left unrecognized or undertreated, it can lead to long-term esophageal damage.

SHORT COMMUNICATION: ORIGINAL ARTICLE: GASTROENTEROLOGY: EOSINOPHILIC GI DISORDERS

Avoidant/Restrictive Food Intake Disorder in Diet-treated Children With Eosinophilic Esophagitis

*[Jacob Robson](#), *[Trevor Laborda](#), ¹[Susan Fitzgerald](#), *[Joseph Andersen](#), ⁴[Kathryn Peterson](#), *[Molly O'Gorman](#), *[Stephen Guthery](#), and ³[Laura Bennett-Murphy](#)

ABSTRACT

Eosinophilic esophagitis (EoE) is an inflammatory condition of the esophagus with rising incidence in children. Owing to potential adverse effects and high costs of EoE medications, strict elimination diets are often employed as a mainstay of long-term EoE therapy in children. Currently, there are no effective tests to pinpoint food protein triggers in children with EoE. Therefore, EoE elimination diets are often broad (including milk, soy, wheat, egg, fish/shellfish, and nuts) and can greatly alter a child's baseline eating habits. Herein, we describe 2 cases of avoidant/restrictive food intake disorder (ARFID) in children with remitted EoE maintained on an elimination diet. We also present comorbidity data on ARFID and diet-treated EoE from our pediatric EoE clinic. This is the first report of disordered eating associated with EoE therapy. As EoE is becoming more common, close monitoring of intake and growth in patients treated with elimination diets will be key.

Key Words: eating disorder, food allergy, food protein-restricted diet, pediatric gastroenterology

(JPGN 2019;69: 57–60)

Although first described only 25 years ago (1), eosinophilic esophagitis (EoE) is now commonly diagnosed in childhood and is a frequent source of referral to pediatric gastroenterology. EoE is driven by a dysregulated, delayed-type T-cell response to repeated food and/or environmental antigen exposures (2). There are no medications approved by the United States Food and Drug

What Is Known

- Eosinophilic esophagitis is a chronic, immune-mediated disease with rising incidence.
- Owing to the cost, lack of long-term data and potential for adverse events, parents of pediatric eosinophilic esophagitis patients commonly express concerns about eosinophilic esophagitis maintenance medications.
- Strict food protein elimination diets are often used as eosinophilic esophagitis maintenance therapy in children.

What Is New

- Avoidant/restrictive food intake disorder is a newly classified eating disorder in the *Diagnostic and Statistical Manual of Mental Disorders*.
- This is the first report of disordered eating related to eosinophilic esophagitis treatment with an elimination diet.
- Children with eosinophilic esophagitis, treated with an elimination diet, have several known risk factors for the development of overly restrictive intake.

RARE DISEASES
CLINICAL RESEARCH NETWORK





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Join Our Contact Registry

It Takes a Village

Table 1. EoE recommendations

Statement	Quality of evidence	Strength of recommendation
<i>Esophageal dilation</i>		
15. We suggest the use of endoscopic dilation as an adjunct to medical therapy as a treatment for esophageal strictures causing dysphagia in patients with EoE	Low	Conditional
<i>Maintenance therapy</i>		
16. We suggest continuation of effective dietary or pharmacologic therapy for EoE to prevent recurrence of symptoms, histologic inflammation, and endoscopic abnormalities	Low	Strong
Monitoring and evaluation of response		
17. We recommend evaluating response to treatment of EoE with assessment of symptomatic and endoscopic and histologic outcomes	Low	Strong
Pediatric-specific considerations		
18. In children with EoE and dysphagia, we suggest an esophagram for evaluation of fibrostenotic disease	Very low	Conditional
19. We suggest evaluation by a feeding therapist and/or dietician as an adjunctive therapeutic intervention in children with EoE and feeding dysfunction	Very low	Conditional

Take Home Points

- EoE is a Type 2 Inflammatory Disease and needs both
 - interruption of T2 inflammatory cascade
 - management of clinical symptoms and psychosocial consequences
- EoE: It takes a village



Thank you!

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