Expert Perspectives on Improving Early Recognition of Eosinophilic Esophagitis and Examining the Potential Clinical Utility of Emerging Targeted Therapy

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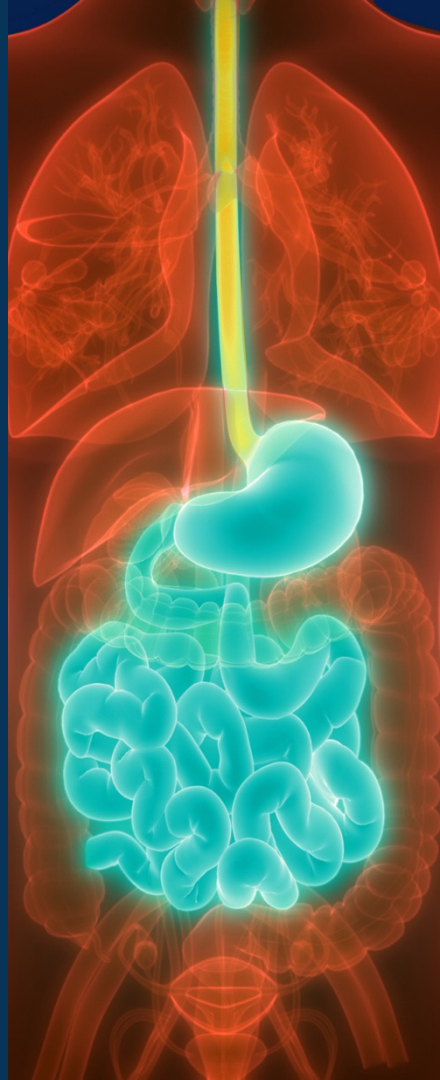

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Let’s Talk Candidly About Eosinophilic Esophagitis

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EoE Defined[1]

"Eosinophilic esophagitis represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation"

1. Liacouras C et al. *J Allergy Clin Immunol.* 2011;128:3-20.e6.

Basic EoE History

1980s	Esophageal eosinophils indicative of reflux esophagitis (Winter et al)
1990/1992	Severe esophageal eosinophilia reported as a problem (Straumann et al)
1995	Diagnosis of eosinophilic esophagitis first presented (Kelly et al)
2003	NASPGHAN first allows eosinophilic esophagitis to be presented as a formal lecture at annual meeting
2004/2005	TIGERS formed
2006/2007	Eosinophilic esophagitis fully accepted by US adult gastroenterologists
2006	First set of eosinophilic esophagitis guidelines presented
2011	Second set of eosinophilic esophagitis guidelines presented
2017	AGREE conference

Landmark Article[1]

GASTROENTEROLOGY 1995;109:1503–1512

Eosinophilic Esophagitis Attributed to Gastroesophageal Reflux: Improvement With an Amino Acid–Based Formula

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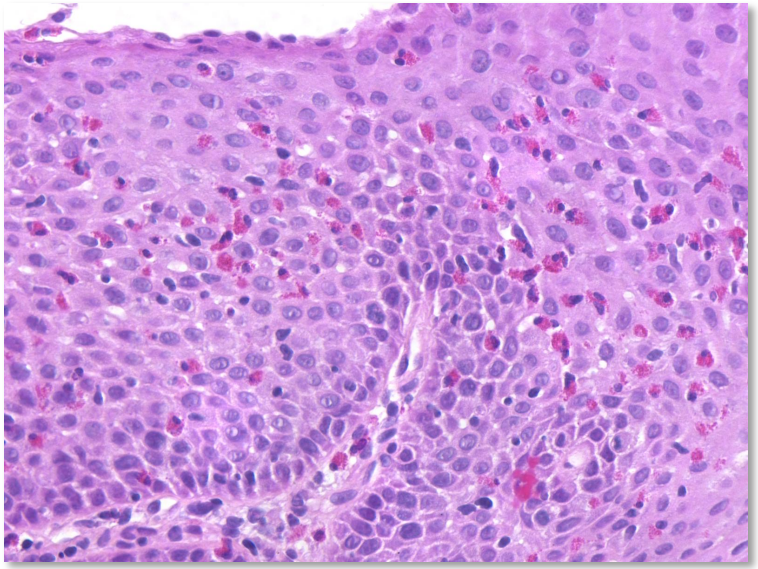
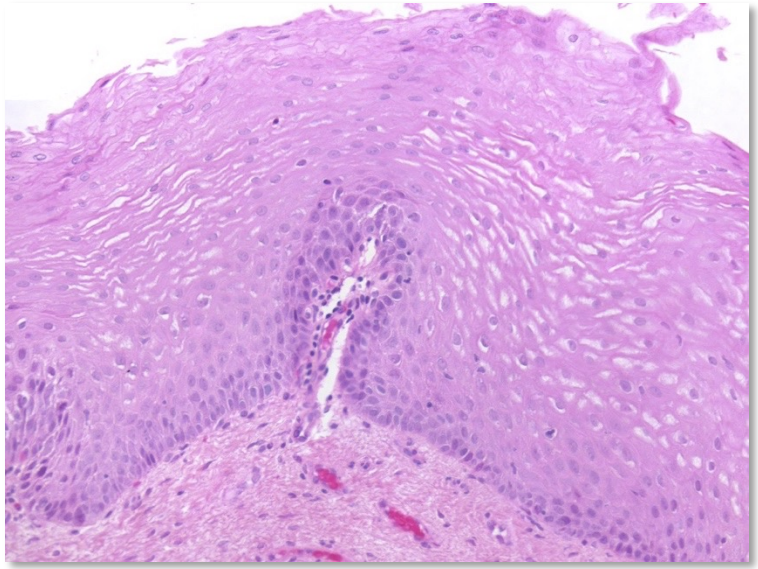
1. Kelly KJ et al. *Gastroenterology*. 1995;109:1503-1512.

EoE: Elemental Diet



Before



After

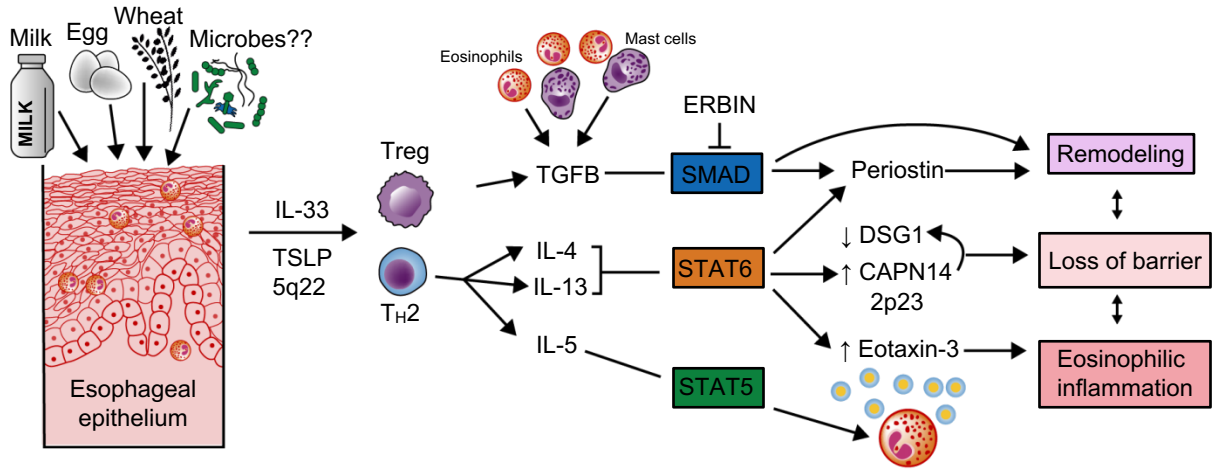
Epidemiology of EoE

- Prevalence is about 1 in 2,000 people in Western countries[1]
- Incidence is estimated at 10 cases per 100,000 individuals annually[1]
- Occurs most often in those aged <50 years of age[2]
  - At least 3 times more common in male patients than in female patients
  - Found in 2%-7% of patients undergoing endoscopy for any reason
  - Found in 12%-23% of patients undergoing endoscopy for dysphagia
- Most common cause of bolus food impaction[2]

1. Dellon ES. *Nat Rev Gastroenterol Heptaol*. 2017;14:479-490. 2. Dellon ES. *Gastroenterol Clin N Am*. 2014;43:201-218.

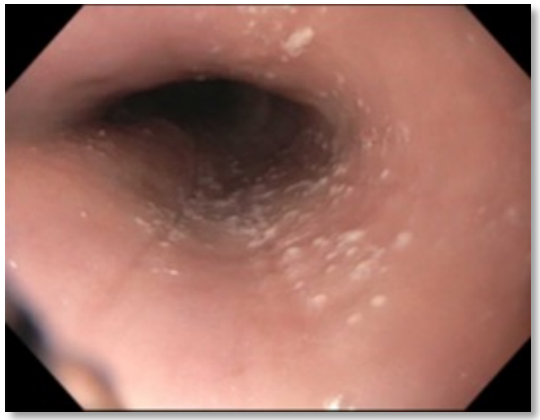
EoE Pathophysiology[1]

- T_H2-mediated condition marked by infiltration of eosinophils into the esophagus
  - Activated T_H2 lymphocytes increase tissue levels of T_H2 cytokines (eg, IL-4, IL-5, and IL-13)
  - Results in chronic esophageal inflammation and dysfunction

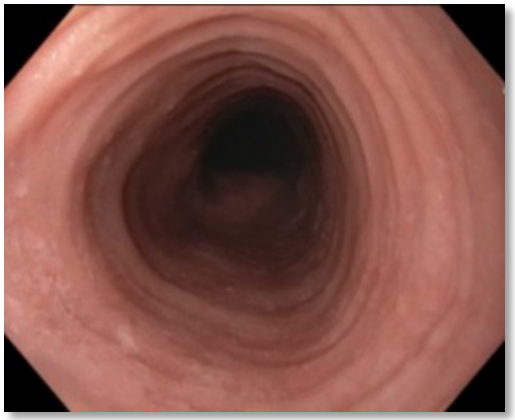


1. O'Shea KM et al. *Gastroenterology*. 2018;154:333-345.

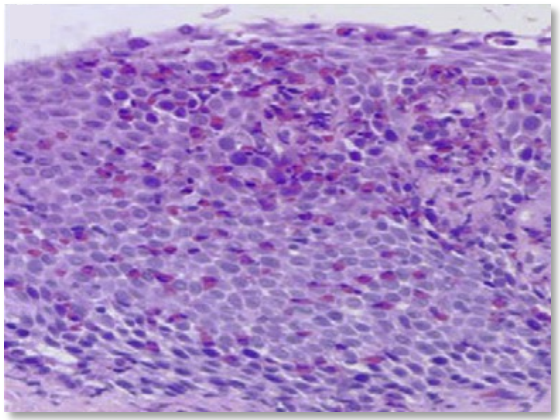
Gold Standard Diagnosis Is …



Edema,
white plaques (exudates),
longitudinal furrows

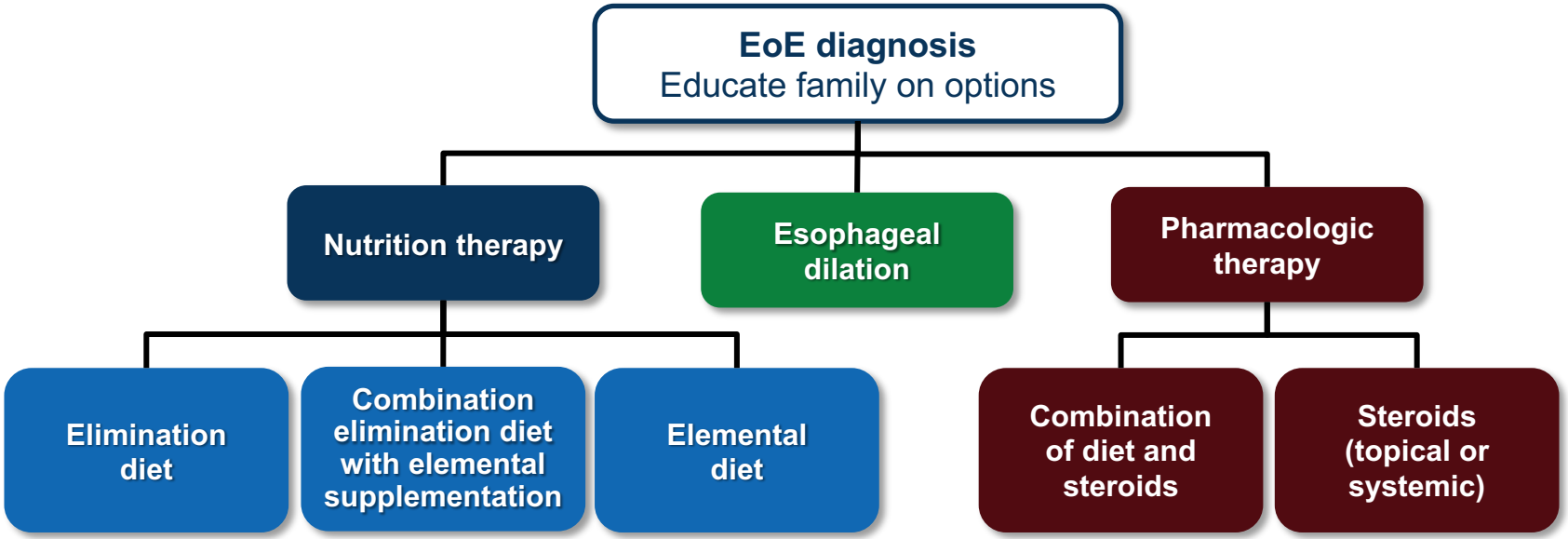


Esophagus with edema
and rings



Management Options for EoE[1]

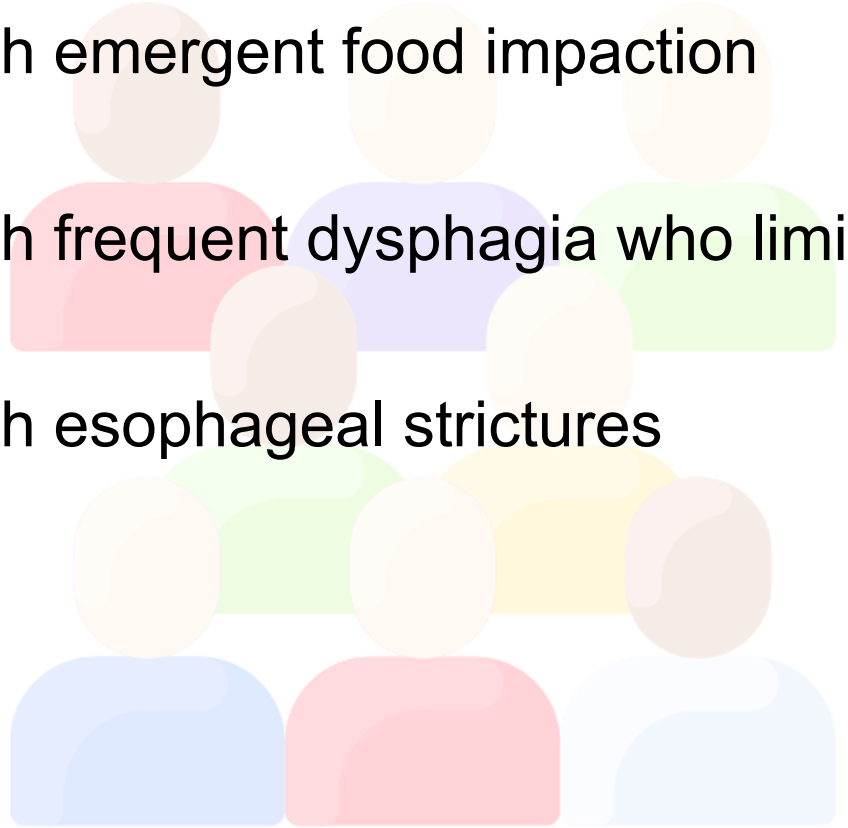
After EoE is diagnosed by clinicians, treatment choices are:



1. Liacouras CA et al. *J Allergy Clin Immunol*. 2011;128:3-20.

In the Adult GI World, EoE is a …

- 48-year-old with emergent food impaction
- 52-year-old with frequent dysphagia who limits food intake
- 56-year-old with esophageal strictures



But Have You Seen a …

- 3-year-old with poor weight gain and feeding difficulty?
- 5-year-old with persistent intermittent vomiting?
- 7-year-old with chronic epigastric pain and regurgitation?
- 8-year-old with frequent heartburn that recurs after stopping a PPI?
- 10-year-old who takes 1+ hours to eat a meal, often drinking a lot of water?
- 12-year-old with complaints of episodes of “difficulty swallowing” but has no evidence of esophageal narrowing?
- 15-year-old with an “emergent” esophageal food impaction requiring immediate removal secondary to esophageal narrowing or stricture?

PPI and Esophageal Eosinophilia

- In the beginning …
  - PPIs ineffective in treating esophageal/reflux-related symptoms
  - Significant esophageal eosinophilia remained = EoE
- 2000s …
  - Adult GIs began to increase rate of biopsies and discovered patients with esophageal eosinophilia, especially in patients presenting with dysphagia
- PPI-REE: antigen-mediated EoE can respond to PPIs irrespective of detectable GERD[1]
- AGREE diagnostic model from 2018

1. Odiase E et al. *Gastroenterology*. 2018;154:1217-1221.e3

Future Medical Treatment

- FDA-accepted swallowed steroid therapy

- Biologic therapy
  - Anti–IL-5
  - Anti–IL-4
  - Anti–IL-13
  - Anti-eotaxin
  - Others

Top 10 EoE Questions in Pediatrics

6 Are there any other methods to diagnose EoE beside routine EGD with biopsy?

7 Can you have both EoE and GERD?

8 Should PPIs still be the first option when treating EoE?

9 Should the patient/family be involved in deciding a specific approach to treatment?

10 Is dietary restriction still an effective therapy?

Top 10 EoE Questions in Pediatrics (Cont'd)

1. Will future biologic therapy improve treatment for EoE?
2. Are there different phenotypes of EoE?
3. Does early diagnosis of EoE help to prevent complications?
4. Should treatment for EoE be ongoing?
5. Are symptoms of dysphagia always associated with esophageal narrowing?

Meet the Experts

What Is the Importance of Early Diagnosis of EoE?

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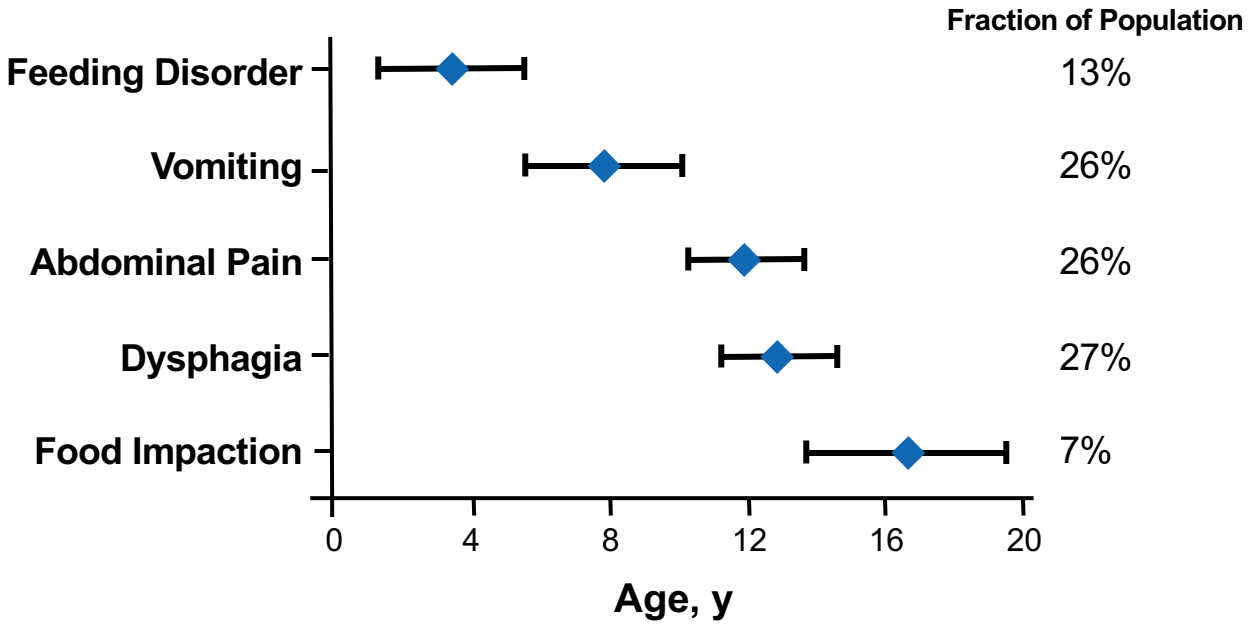
EoE Signs and Symptoms Vary Among Children and Adults

- **Children**[1-3]
  - Feeding problems, failure to thrive
  - Abdominal pain, nausea, vomiting
  - Heartburn, regurgitation
  - Endoscopic findings of inflammation (exudates, furrows, edema)
- **Adolescents**[2-4]
  - Heartburn, regurgitation
  - Dysphagia
  - Esophageal narrowing
- **Older adults**[2-4]
  - Heartburn, chest discomfort
  - Food impaction, dysphagia typically predominate
  - Endoscopic findings of fibrostenosis (rings, strictures, narrowing)

1. Dellon ES. *Dig Dis*. 2014;32:48-53. 2. Nguyen N et al. *Gastroenterol Hepatol*. 2015;11:670-674. 3. Straumann A et al. *Gastroenterology*. 2018;154:346-359.
4. Dellon ES et al. *Clin Gastroenterol Hepatol*. 2014;12:589-596.

EoE Presentation by Age[1]

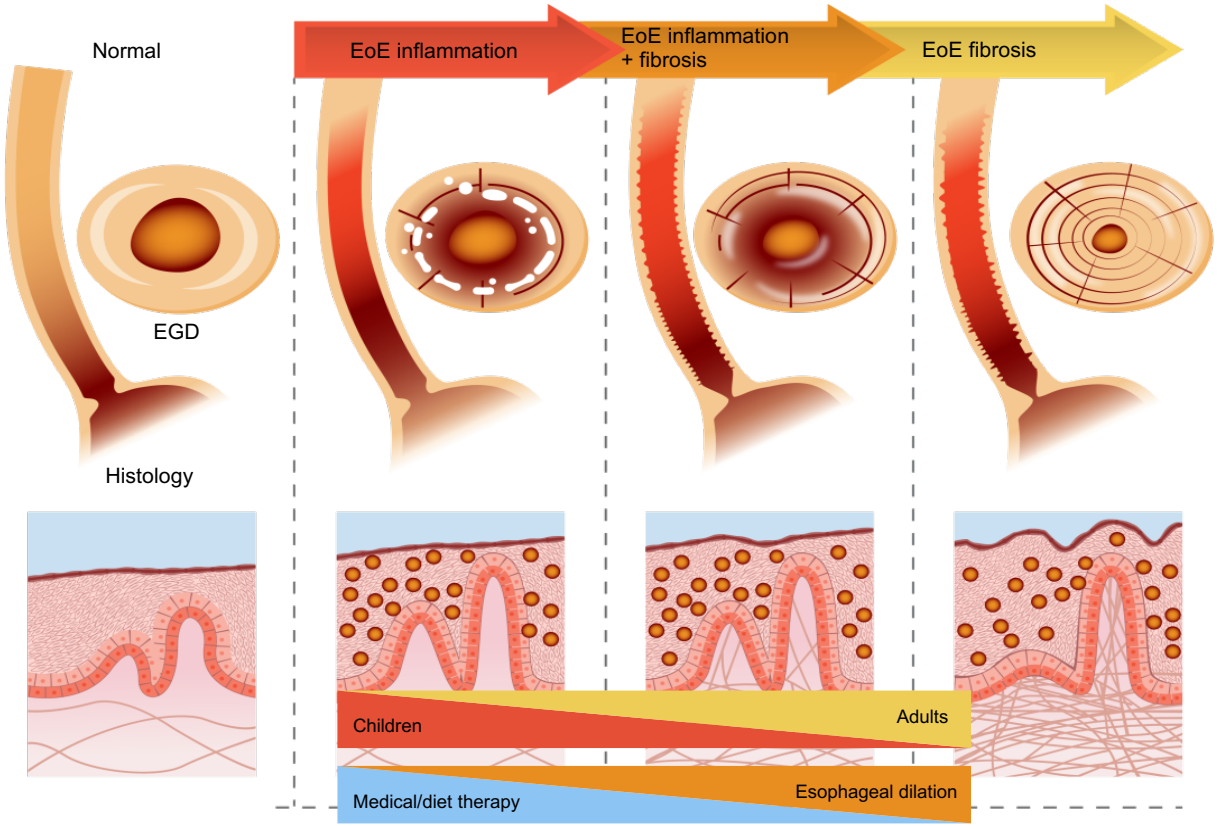


1. Noel RJ et al. *N Engl J Med*. 2004;351:940-941.

Association of Atopy With EoE

Reference	Patients, N	Age	Asthma	Allergic Rhinitis	Atopic Dermatitis	Food Allergy
General population	—	—	10%	20%-40%	5%-20%	1%-6%
Spergel	620	8 m - 20 y	50%	61%	21%	16%
Assa'ad	89	3 m - 18 y	39%	30%	19%	9%
Sugnanam	45	3 m - 16 y	66%	93%	55%	24%
Guajardo	39	1 m - 31 y	38%	64%	26%	23%
Roy-Ghanata	23	18 y - 57 y	26%	78%	4%	—

Consequences of EoE: Inflammation and Remodeling[1]



1. Dellon ES, Hirano I. *Gastroenterology*. 2018;154:319-332.e3.

Diagnosis of EoE Can Be Challenging …

- Symptoms are nonspecific to EoE[1]
  - Diagnosis per guidelines is based on symptoms, histology, and excluding other causes of EoE; presence of endoscopy features is supportive
- Presence of eosinophils in the esophagus may not be indicative of EoE[2]
  - The differential diagnosis of esophageal eosinophilia needs to be considered
- Symptoms often **DO NOT CORRELATE** with histologic/tissue disease
- Although endoscopy is invasive, expensive, and typically requires sedation[3], it is currently the "gold standard" for disease diagnosis

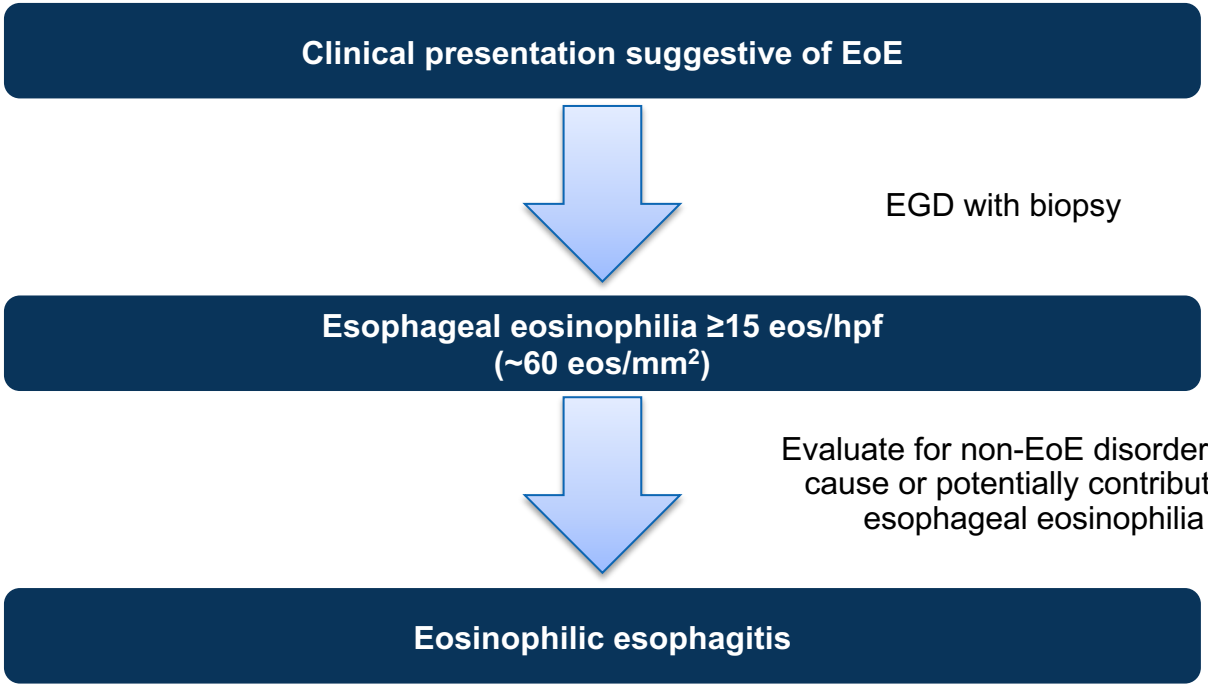
1. Dellon ES. *Dig Dis*. 2014;32:48-53. 2. Straumann A et al. *Gastroenterology*. 2018;154:346-359. 3. Dellon ES et al. *Gastroenterology*. 2018;155:1022-1033.

… But Early Diagnosis Is Important[1-4]

- Uncontrolled, EoE can lead to …
  - Esophageal stricture
    - 52% of patients with a diagnostic delay had food impactions and 57% had a stricture
  - Feeding dysfunction (especially relevant for children)
    - Anywhere between 14% and 60% of patients with EoE develop feeding dysfunction
    - 21% of children with EoE who had feeding disorders also had failure to thrive
  - Negative impact on quality of life

1. Muir A et al. *Clin Exp Gastroenterol*. 2019;12:391-399. 2. Warners MJ et al. *Am J Gastroenterol*. 2018;113:836-844. 3. Hommel KA et al. *Pediatr Allergy Immunol*. 2012;23:494-499. 4. Schoepfer AM et al. *Gastroenterology*. 2013;145:1230-1236.e1-2.

Updated EoE Diagnostic Algorithm (AGREE)[1]



1. Dellon ES et al. *Gastroenterology*. 2018;155:1022-1033.

PPI-Responsive EoE (REE) — Estimates[1]

Author	Year	Population	Design	Patients With Eosinophilia Treated With PPI, n	PPI-REE, n (%)
Dranove	2009	Ped	Retrospective	43	17 (40)
Sayej	2009	Ped	Retrospective	36	14 (39)
Molina-Infante	2011	Adult	Prospective	35	26 (74)
Peterson	2010	Adult	RCT	12	4 (33)
Moawad	2011	Adult	RCT	20	7 (35)
Dellon	2013	Adult	Prospective	65	24 (37)
Schroeder	2013	Ped	Retrospective	7	5 (71)

1. Dohil R et al. *Dig Dis Sci.* 2012;57:1413-1419.

The PPI Diagnostic Dilemma

- PPIs are known to treat acid-based disease in patients with symptoms of reflux
- Historically, lack of response to PPIs was used to distinguish EoE from GERD[1]
- EoE and PPI-REE have similar clinical, endoscopic, histologic, and gene expression features[1]

Another Dilemma

- Some patients with esophageal eosinophilia who are unresponsive to diet or steroids respond to PPI therapy
- Some patients with EoE who are treated successfully with elimination diets respond to PPIs when those diets are stopped[1]
- Finally, GERD and EoE can exist simultaneously[2]

1. Odiase E et al. *Gastroenterology*. 2018;154:1217-1221.e3. 2. Goyal A et al. *World J Gastrointest Pharmacol Ther*. 2016;7:21-32.

Evolving Approach to PPIs[1-4]

- High response rates (40%-50%) to PPIs in patients who appear to otherwise have EoE
  - Clinical, endoscopic, histologic, immunologic, and molecular features at baseline (pre-PPI) do not appear to distinguish or predict who may respond to a PPI
- Potential non-acid mediated mechanism of PPIs
  - Suppress T_H2-mediated eotaxin-3 secretion
  - Improve esophageal barrier function
- AGREE guidelines: removal of PPIs from the diagnostic algorithm
- When to use PPIs is still controversial

1. Molina-Infante J et al. *Gut*. 2016;65:524-531. 2. Eluri S et al. *Curr Opin Gastroenterol*. 2015;31:309-315. 3. Wen T et al. *J Allergy Clin Immunol*. 2014;137:919-921.
4. Cheng E et al. *Gut*. 2013;62:824-832.

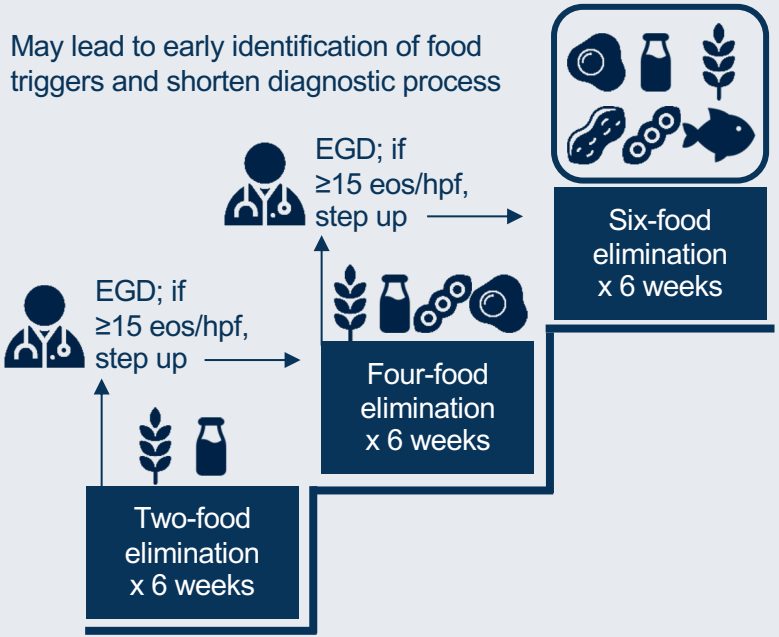
Elimination Diets: What to Eliminate

	Six-Food (SFED)	Four-Food (FFED)	Two-Food	One-Food
Cow milk	✓	✓	✓	✓
Wheat	✓	✓	✓	
Egg	✓	✓		
Soy	✓	✓		
Peanut/tree nut	✓			
Fish/seafood	✓			

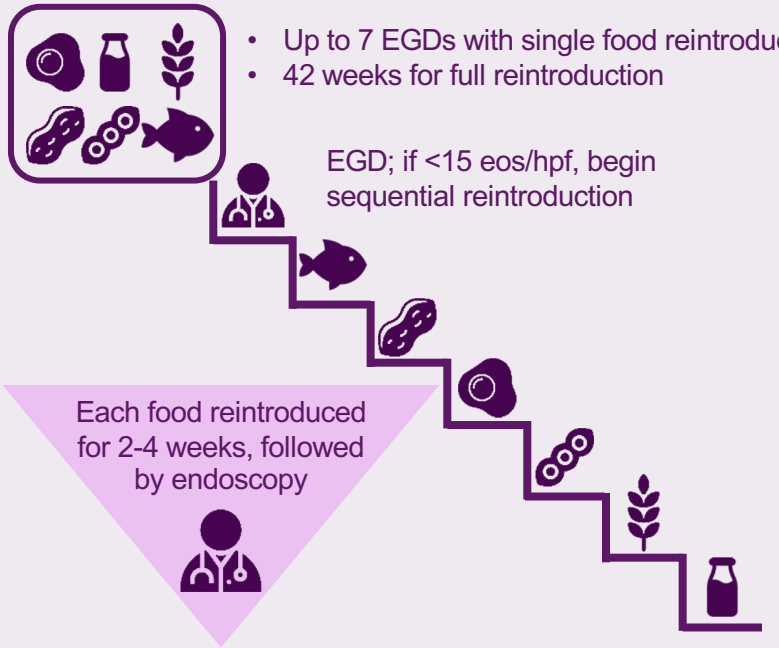
Diet Therapy for EoE[1]

Step-Up Elimination Diet

- May lead to early identification of food triggers and shorten diagnostic process



Step-Down Six-Food Elimination Diet



1. Patel R, Hirano I. Eosinophilic esophagitis: Frequently asked questions (and answers) for the early-career gastroenterologist. *New Gastroenterologist*. August 1, 2020.

Challenge the Experts

How Will Emerging Targeted Therapies Change the Management of EoE?

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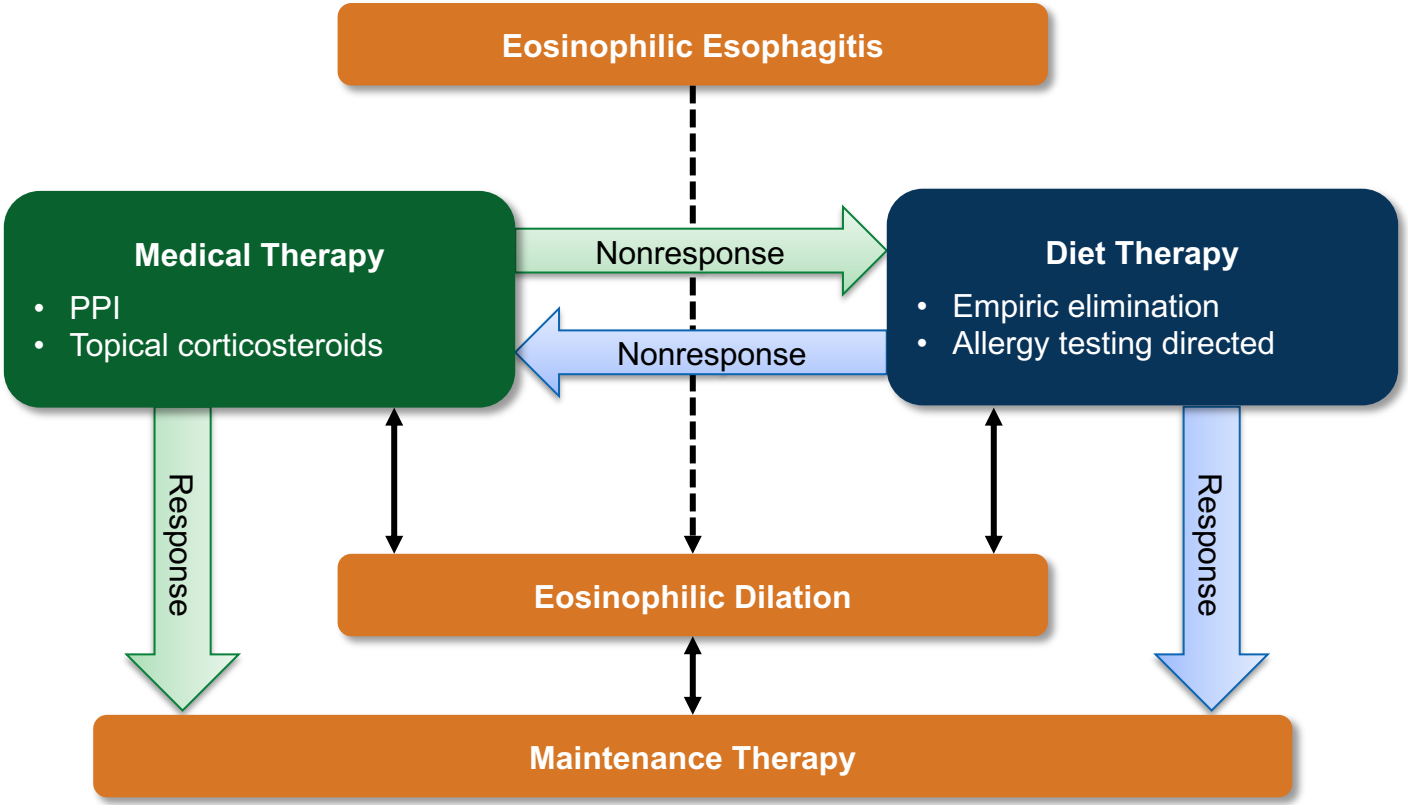
EoE Management[1]

- Treatment goals
  - Symptom control
  - Control inflammation (<15 eos/hpf) and esophageal remodeling
- Not enough to just look for histologic improvement
  - Discrepancies between histological and symptomatic remission
- EoE is chronic and needs long-term treatment

1. Abe Y et al. *Clin J Gastroenterol*. 2017;10:87-102.

EoE Suggested Approach to Management Algorithm[1]



1. Hirano I. *Gastroenterology*. 2018;155:601-606.

Treat to Target[1]


Symptoms
Resolution of dysphagia without the need to avoid food based on texture


Histopathology
Resolution of esophageal eosinophilic inflammation (<5-15 eos/hpf)


Endoscopy
Improvement in inflammatory features and strictures (diameter >15 mm)

1. Hirano I et al. *Gastroenterology*. 2020;158:840-851.

Current EoE Treatments

Nonpharmacologic

- Dietary elimination
  - Elemental formula
  - Empiric elimination
  - Targeted elimination
- Esophageal dilation

No FDA-approved medications for EoE

Pharmacologic

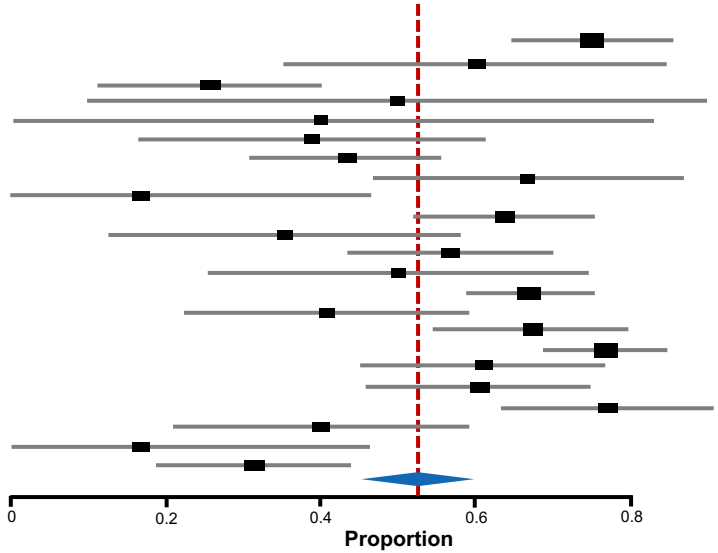
- Proton pump inhibitors
- Corticosteroids
  - Systemic
  - Swallowed/topical (standard + novel formulations)
- Leukotriene antagonists
- Mast cell stabilizers
- Immunomodulators
- Biologics
- Small molecules

Updated AGA/JTF Guideline Recommendation: PPIs[1]

Recommendation: In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using PPI over no treatment (conditional recommendation, very low–quality evidence)

Forest Plot for Not Achieving Histologic Remission

Studies	Estimate	95% CI	Ev/Trt
Garrean 2009	0.750	0.644-0.856	40/64
Peterson 2010	0.600	0.352-0.848	9/15
Molina-Infante 2011	0.257	0.112-0.402	9/35
Abe 2011	0.500	0.100-0.900	3/6
Fujiwara 2012	0.400	0.000-0.829	2/5
Francis 2012	0.389	0.164-0.614	7/19
Vazquez-Elizondo 2013	0.433	0.308-0.559	26/60
Moawad 2013	0.667	0.465-0.868	14/21
Lee 2013	0.167	0.000-0.465	1/6
Dellon 2013	0.636	0.520-0.752	42/66
Mangla 2014	0.353	0.126-0.580	6/17
Molina (2) 2014	0.566	0.433-0.699	30/53
van Rhijn 2014	0.500	0.255-0.745	8/16
Gomez-Torrijos 2016	0.669	0.586-0.753	81/121
Jiao 2016	0.407	0.222-0.593	11/27
Savarino 2017	0.673	0.546-0.801	35/52
Philpott 2016	0.766	0.686-0.847	82/107
Sayej 2009	0.611	0.452-0.770	22/36
Dranove 2010	0.605	0.459-0.751	26/43
Schroeder 2013	0.771	0.632-0.911	27/35
Rea 2013	0.400	0.208-0.592	10/25
Dhaliwal 2014	0.167	0.000-0.465	1/6
Gutierrez-Junquera 2016	0.314	0.186-0.441	16/51
Overall (I^2 = 81%, *P* < .001)	**0.526**	**0.450-0.601**	**516/885**



Notes: Certainty in evidence rated down for single-arm cohort studies and high inconsistency (I^2 = 81%) that may be related to study design and patient selection. Absolute effect size difficult to estimate

1. Hirano I et al. *Gastroenterology.* 2020;158:840-851.

Swallowed Topical Corticosteroids

- **Concept:** Provide a topical coating of an anti-inflammatory agent to the esophagus
- Multiple RCTs demonstrate benefits of topical steroids in children and adults[1]
  - Most studies use budesonide or fluticasone
  - Need knowledge of the proper use and dosing of each agent
  - Risk of oral candidiasis for all topical steroids
- The only "strong recommendation" in the 2020 AGA/JTF guidelines supports the use of topical glucocorticosteroids over no treatment[2]
- Symptoms may recur with treatment discontinuation
  - Assess efficacy with follow-up endoscopy after 6-12 weeks of therapy[3]

1. Straumann A et al. *Gastroenterology*. 2018;154:346-359. 2. Hirano I et al. *Gastroenterology*. 2020;158:1776-1786.
3. Abe Y et al. *Clin J Gastroenterol*. 2017;10:87-102.

Topical Corticosteroids

- **Fluticasone propionate[1]**
  - Traditionally used from a multidose inhaler: puffed directly into the mouth and swallowed
  - Recommended dose: 440-880 mcg twice daily for 8 weeks in adults
  - Need for strict adherence to instructions to optimize efficacy
- **Viscous budesonide[2,3]**
  - Aqueous budesonide mixed with a thickener and swallowed
  - Evidence suggests more complete histologic remission with oral viscous budesonide vs nebulized/inhaled formulation[2]
    - More extensive contact with esophageal mucosa[2]

1. Velikova T. *Gastroenterolgoy Rev*. 2020;15:27-33. 2. Dellon ES et al. *Gastroenterology*. 2012;143:221-324. 3. Rawla P et al. *Drugs R D*. 2018;18:259-269.

Maintenance Therapy[1]

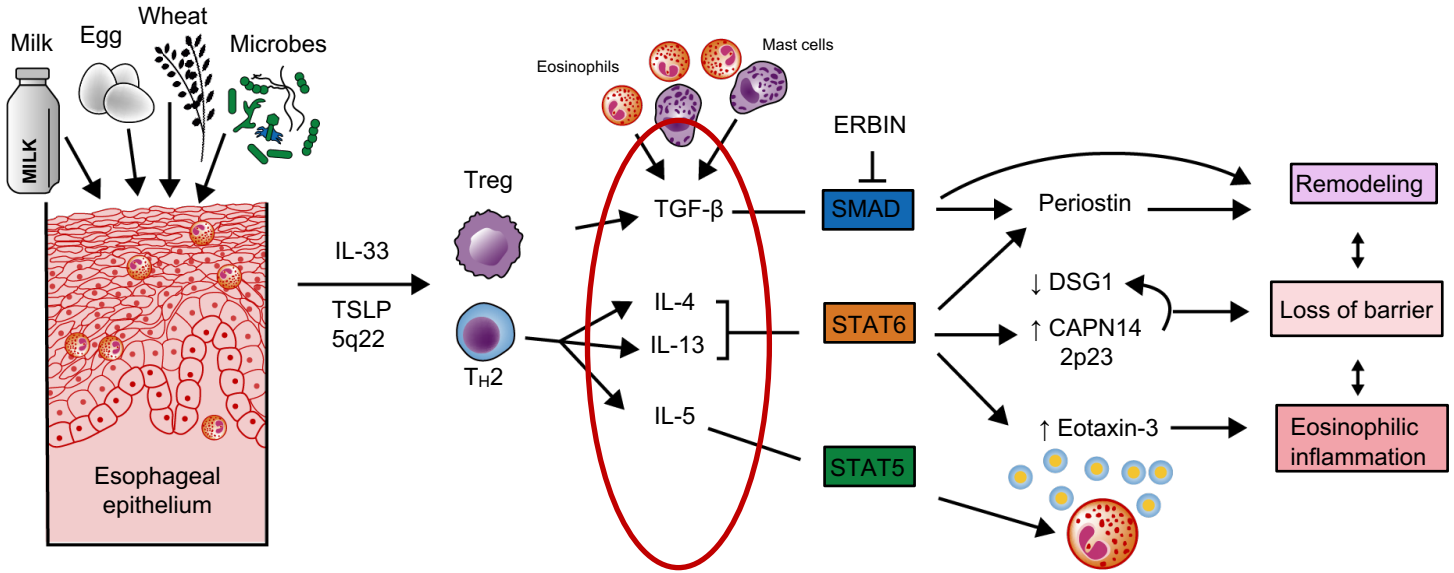
- EoE is a chronic disease; when treatment is stopped, the disease activity recurs, typically rapidly
- Ongoing maintenance therapy should be considered in all patients
- Indicated when there is evidence of chronic remodeling, recurrent food impaction, severe symptoms, or rapid return of symptoms when off therapy
- More data on long-term outcomes and maintenance therapies are needed

1. Velikova T. *Gastroenterology Rev*. 2020;15:27-33.

Esophageal Dilation

- Recommended in the AGA/JTF guidelines to address dysphagia associated with esophageal strictures associated with EoE
- Provides immediate and long-lasting relief of dysphagia
  - Patients who have esophageal strictures or narrowing despite drug/diet therapy
  - Reasonable initial treatment for patients with high-grade strictures
- Disadvantages
  - Risks of perforation and bleeding, but uncommon (<1%)
  - Does not address underlying inflammatory process
  - Postprocedural retrosternal pain in the majority of cases

Physiologic Targets of Biologic Therapy in EoE[1]



1. O'Shea KM et al. *Gastroenterology*. 2018;154:333-345.

Why Biologics for EoE?

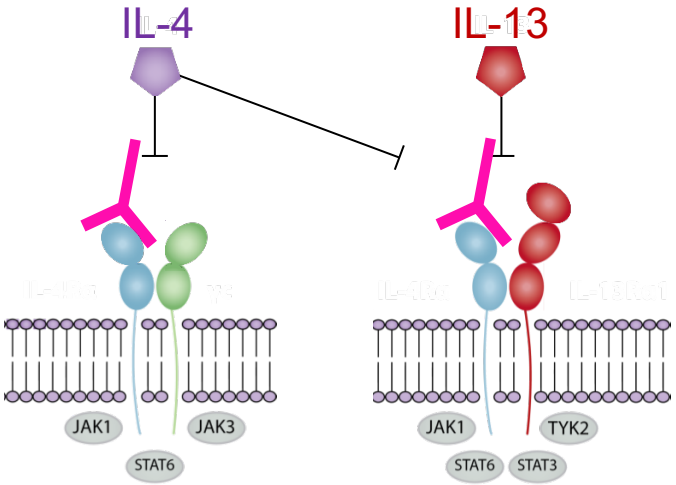
- Corticosteroid-refractory patients or corticosteroid intolerance
- Concept of therapy targeting specific allergic pathways
- Systemic treatment of multiple forms of atopy
- Potential benefits of esophageal remodeling and inflammation
- Practical benefits of intermittent, rather than daily, therapy

AGA/JTF Guidelines: Management of EoE[1]

Biologic Therapies: Anti-IgE	**Biologic Therapies:** Anti–IL-5	**Biologic Therapies:** Anti–IL-13	**Biologic Therapies:** Montelukast, Cromolyn, Immunomodulator, Anti-TNF
Recommendation: In patients with EoE, the AGA/JTF suggests against the use of anti-IgE therapy (conditional recommendation; very low–quality evidence)	**Recommendation:** In patients with EoE, the AGA/JTF recommends using anti–IL-5 therapy only in the context of a clinical trial (no recommendation; knowledge gap)	**Recommendation:** In patients with EoE, the AGA/JTF recommends using anti–IL-13 or anti–IL-4 receptor alpha therapy only in the context of a clinical trial (no recommendation; knowledge gap)	**Recommendation**: In patients with EoE, the AGA/JTF suggests using montelukast, cromolyn sodium, immunomodulators, and anti-TNF only in the context of a clinical trial (no recommendation; knowledge gap)

1. Hirano I et al. *Gastroenterology*. 2020;158:1776-1786.

Dupilumab: Anti–IL-4Rα[1,2]



Type I receptor

B cells, T cells, monocytes, eosinophils, fibroblasts

Type II receptor

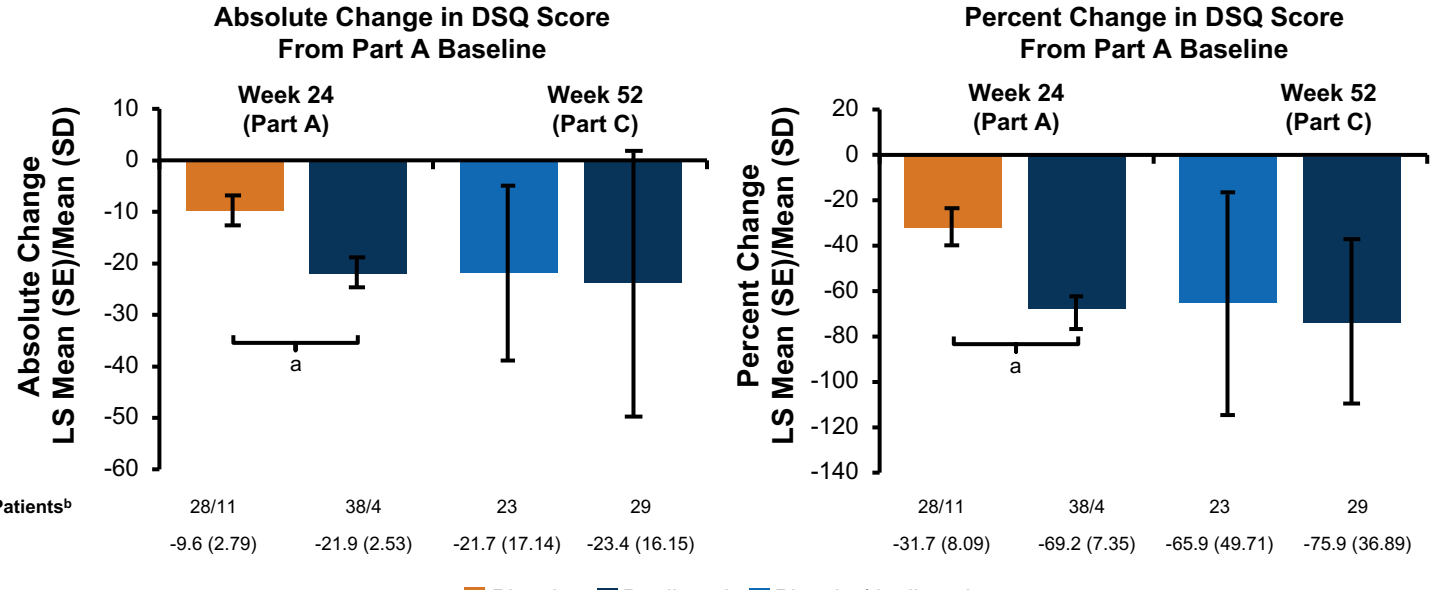
Epithelial cells, smooth muscle cells, fibroblasts, monocytes, activated B cells

- Inhibits signaling of both IL-4 and IL-13
- Approved in the United States for treatment of:
  - Moderate to severe AD (age 6+)
  - Moderate to severe asthma (age 6+)
  - Chronic rhinosinusitis with nasal polyps (age 18+)
- Granted Breakthrough Therapy Designation for EoE by the FDA in September 2020

1. Dupixent (dupilumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761055s035lbl.pdf.
2. Gittler JK et al. *J Allergy Clin Immunol*. 2012;130:1344-1354.

Dupilumab Reduces Dysphagia Symptoms at Weeks 24 and 52[1]

Results From Parts A and C of Phase 3 LIBERTY EoE TREET in Adults and Adolescents With EoE



	Absolute Change				Percent Change			
No. of Patients/Imputed Patients[b]	28/11	38/4	23	29	28/11	38/4	23	29
LS Mean (SE)/Mean (SD)[c]	-9.6 (2.79)	-21.9 (2.53)	-21.7 (17.14)	-23.4 (16.15)	-31.7 (8.09)	-69.2 (7.35)	-65.9 (49.71)	-75.9 (36.89)

Placebo Dupilumab Placebo/dupilumab

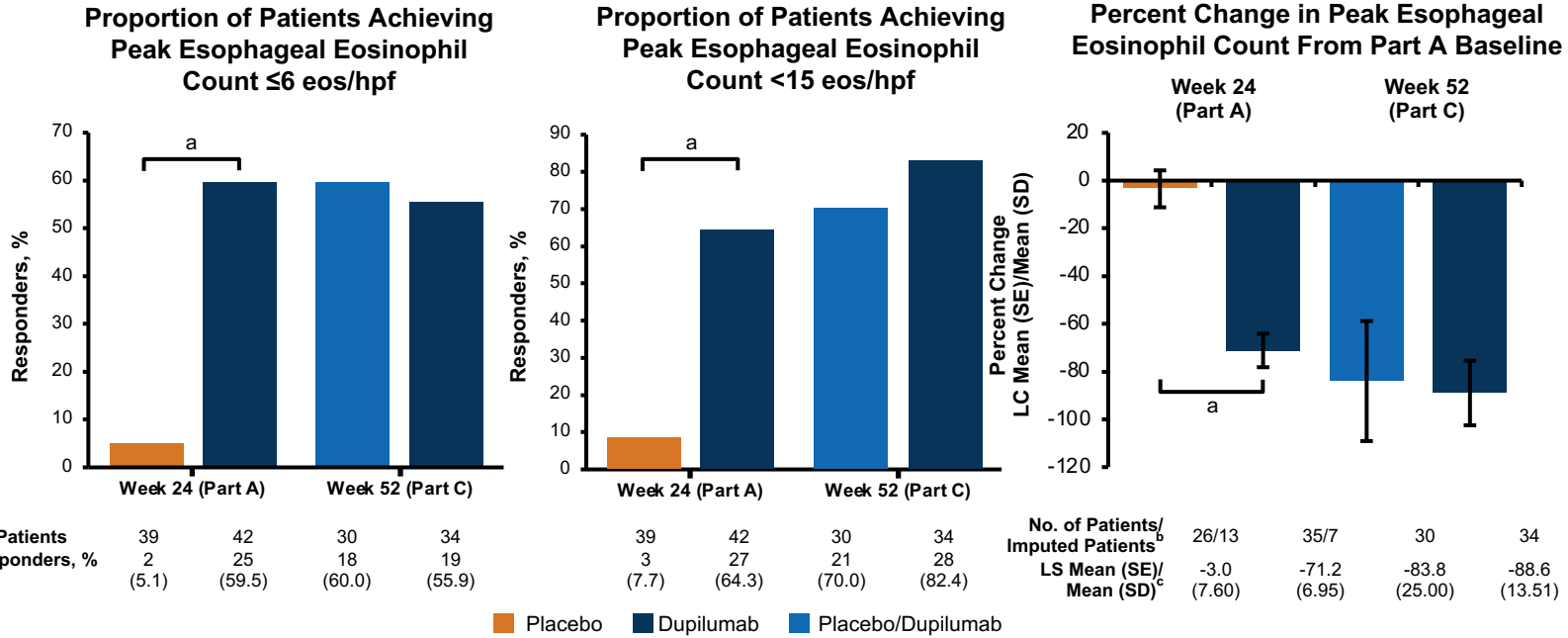
Part A baseline DSQ score, mean (SD) PBO: 35.1 (12.11) DPL: 32.2 (12.66)

[a] $P < .001$. [b] 5 patients in the placebo group received rescue treatment; data after rescue treatment were set to missing and their week-24 data were imputed. Other reasons for missing week 24 DSQ score include early discontinuation from study before week 24 or patients not having daily DSQ scores for ≥8 out of 14 days prior to week 24. No imputation methods were performed for Part C. [c] LS mean (SE) calculated for Part A; mean (SD) calculated for Part C. DSQ scores range from 0-84 with a lower score indicating less frequent or less severe dysphagia. Absolute change in DSQ score from baseline to week 24 was a co-primary endpoint.

1. Dellon ES. Presented at UEG and ACG 2021.

Dupilumab Reduces Peak Intraepithelial Esophageal Eosinophil Counts at Weeks 24 and 52[1]

Results From Parts A and C of Phase 3 LIBERTY EoE TREET in Adults and Adolescents With EoE



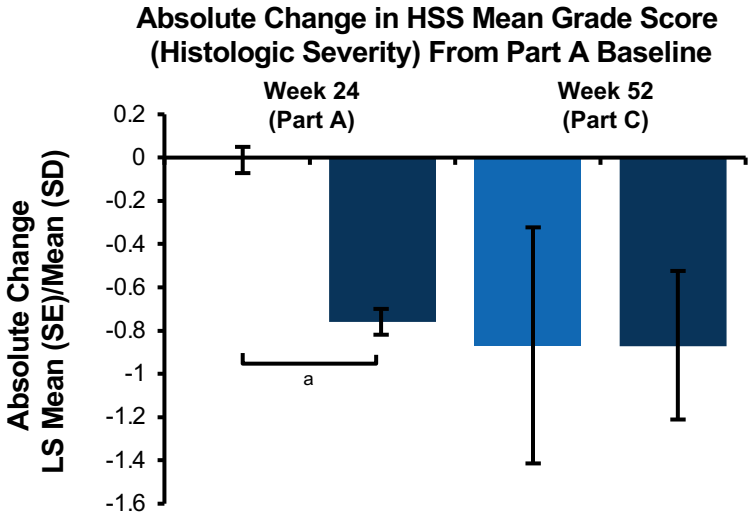
Part A baseline eos/hpf, mean (SD) PBO: 96.5 (54.69) DPL: 82.6 (41.02)

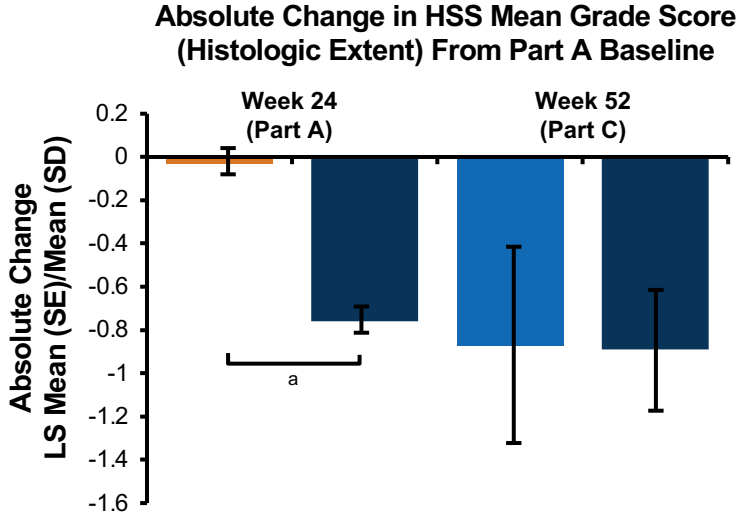
[a] $P < .001$. [b] Five patients in the placebo group received rescue treatment; data after rescue treatment were set to missing and their week-24 data were imputed. No imputation methods were performed for Part C. [c] LS mean (SE) calculated for Part A; mean (SD) calculated for Part C. Proportion of patients achieving peak esophageal intra-epithelial eosinophil count of ≤6 eos/hpf at week 24 was a co-primary endpoint.

1. Dellon ES. Presented at UEG and ACG 2021.

Dupilumab Reduces Severity and Extent of Histologic Features of EoE at Weeks 24 and 52[1]

Results From Parts A and C of Phase 3 LIBERTY EoE TREET in Adults and Adolescents With EoE





No. of Patients/Imputed Patients[b]	26/13	35/7	30	34
LS Mean (SE)/Mean (SD)[c]	-0.001 (0.06)	-0.761 (0.06)	-0.87 (0.55)	-0.87 (0.35)

Placebo Dupilumab Placebo/dupilumab

Part A baseline HSS grade, mean (SD) PBO: 1.3 (0.41) DPL: 1.3 (0.41)

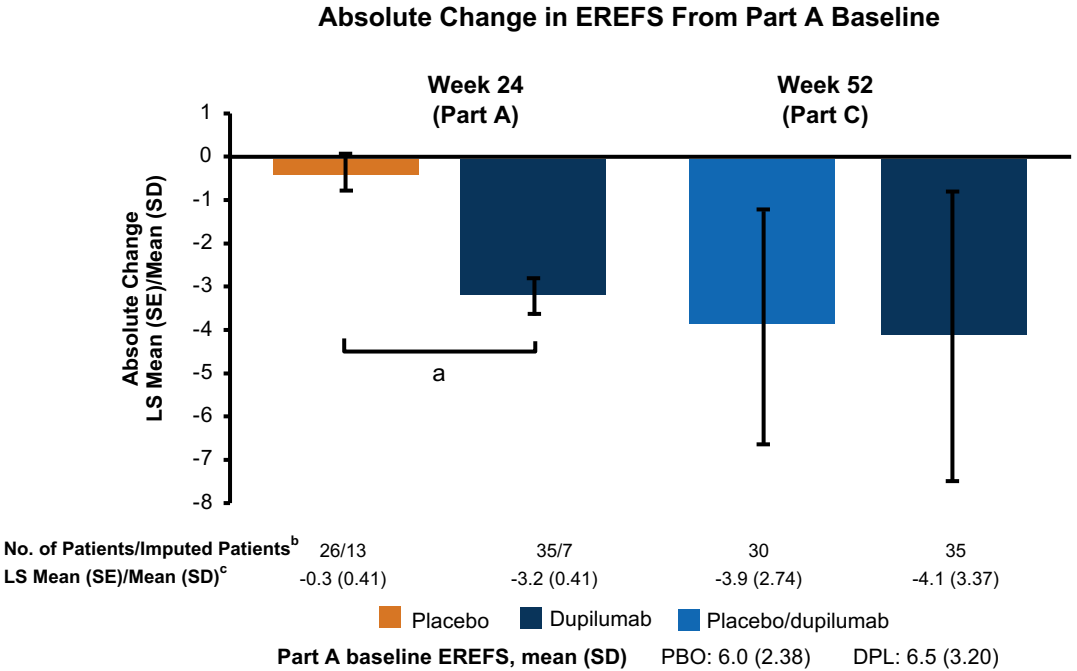
Part A baseline HSS stage, mean (SD) PBO: 1.4 (0.40) DPL: 1.3 (0.33)

[a] $P < .001$. [b] Five patients in the placebo group received rescue treatment; data after rescue treatment were set to missing and their week-24 data were imputed. No imputation methods were performed for Part C. [c] LS mean (SE) calculated for Part A; mean (SD) calculated for Part C. Histologic Scoring System scale ranges from 0-3 with higher scores indicating more severe histologic findings.

1. Dellon ES. Presented at UEG and ACG 2021.

Dupilumab Reduces Endoscopic Features of EoE at Weeks 24 and 52[1]

Results From Parts A and C of Phase 3 LIBERTY EoE TREET in Adults and Adolescents With EoE



[a] $P < .001$. [b] Five patients in the placebo group received rescue treatment; data after rescue treatment were set to missing and their week-24 data were imputed. No imputation methods were performed for Part C. [c] LS mean (SE) calculated for Part A; mean (SD) calculated for Part C. EREFS score ranges from 0-18 with higher scores indicating higher severity/presence.

1. Dellon ES. Presented at UEG and ACG 2021.

Dupilumab Is Generally Well Tolerated at Weeks 24 and 52[1]

Results From Parts A and C of LIBERTY EoE TREET in Adults and Adolescents With EoE

Patients With Event, n (%)	Part A		Part C (Patients From Part A)	
	Placebo (n = 39)	Dupilumab 300 mg QW (n = 42)	Placebo/dupilumab (n = 37)	Dupilumab/dupilumab (n = 40)
Deaths	0	0	0	0
TEAEs	32 (82.1)	36 (85.7)	27 (73.0)	24 (60.0)
Treatment-emergent SAEs	0	2 (4.8)[a]	1 (2.7)[b]	0
TEAEs leading to discontinuation	0	1 (2.4)[c]	2 (5.4)[d]	0
TEAEs occurring in ≥10% of patients in any group				
Injection-site reaction	4 (10.3)	7 (16.7)	8 (21.6)	4 (10.0)
Nasopharyngitis	4 (10.3)	5 (11.9)	3 (8.1)	1 (2.5)
Injection-site erythema	5 (12.8)	3 (7.1)	5 (13.5)	4 (10.0)
Headache	4 (10.3)	2 (4.8)	2 (5.4)	3 (7.5)
Rash	4 (10.3)	0	0	1 (2.5)

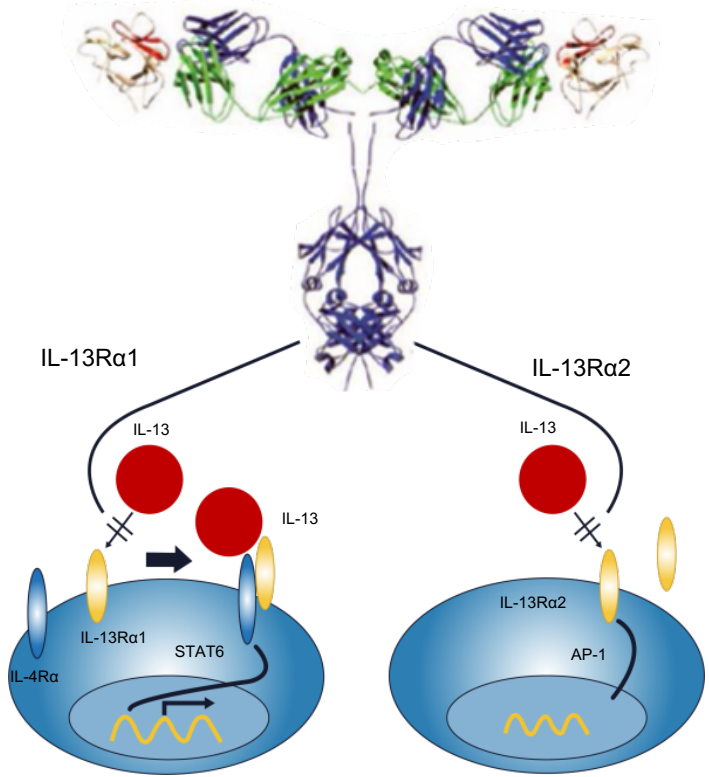
In Part A, five placebo and zero dupilumab patients received rescue treatment; no new patients initiated rescue treatment in Part C

[a] Abdominal pain and uterine polyp assessed as not related to study medication. [b] Shortness of breath and diaphoresis. [c] Arthralgia.
[d] Arthralgia and systemic inflammatory response syndrome.

1. Dellon ES. Presented at UEG and ACG 2021.

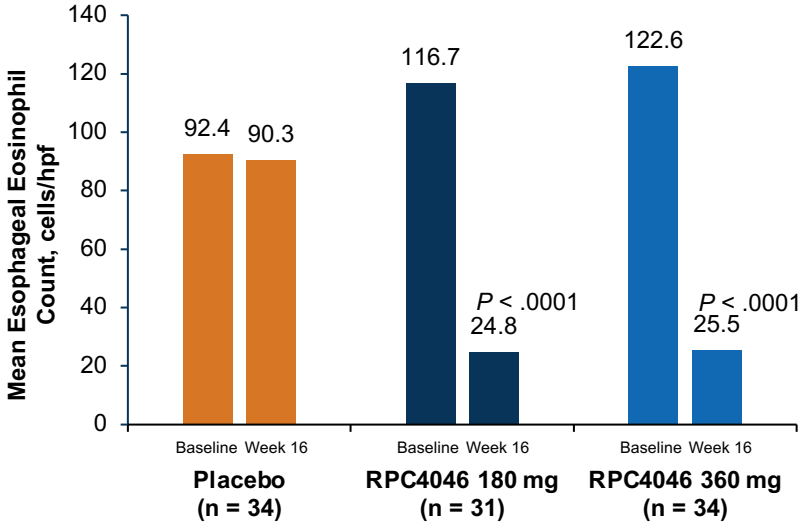
Cendakimab (RPC4046): Anti–IL-13

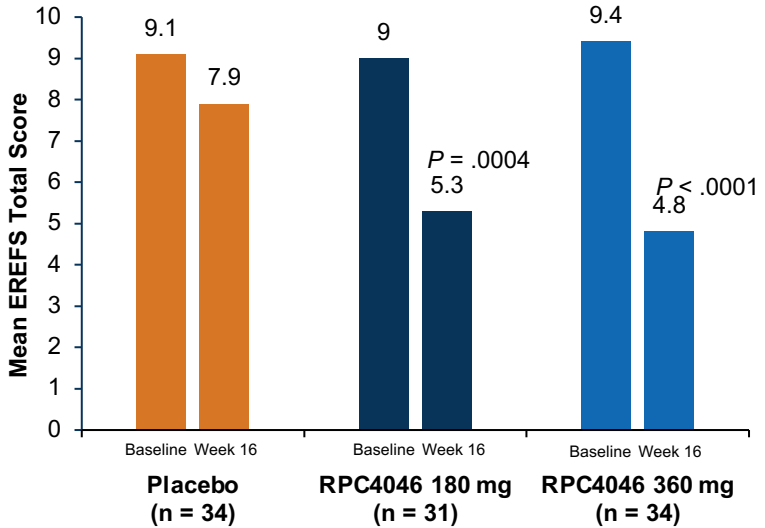
- Recombinant, humanized monoclonal (IgG1k) antibody, highly selective for IL-13
- Inhibits binding of IL-13 to the IL-13Rα1 and IL-13Rα2 receptors
- Administered as a weekly subcutaneous injection



Cendakimab (RPC4046): Anti–IL-13[1] (Cont'd)

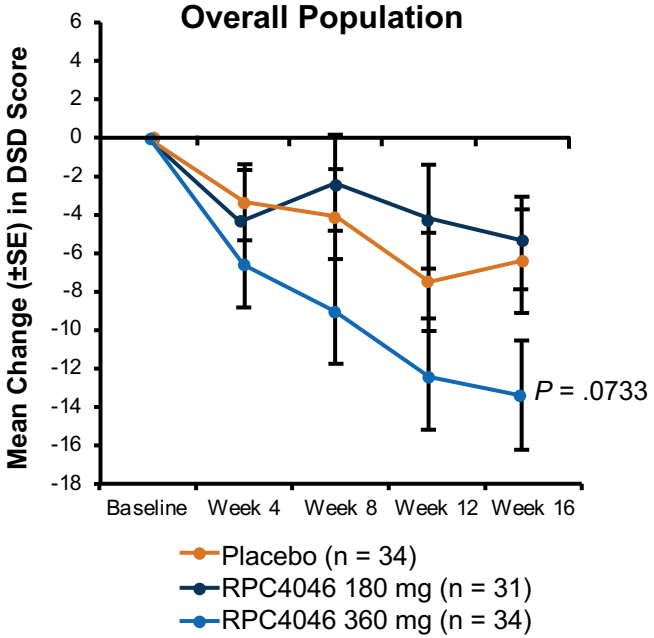
- Randomized, double-blind, placebo-controlled trial in 99 patients (aged 18-65 years)
- 16-week treatment: RPC4046 180 mg or 360 mg subQ versus placebo
- **Primary endpoint:** Change in mean esophageal eosinophil count

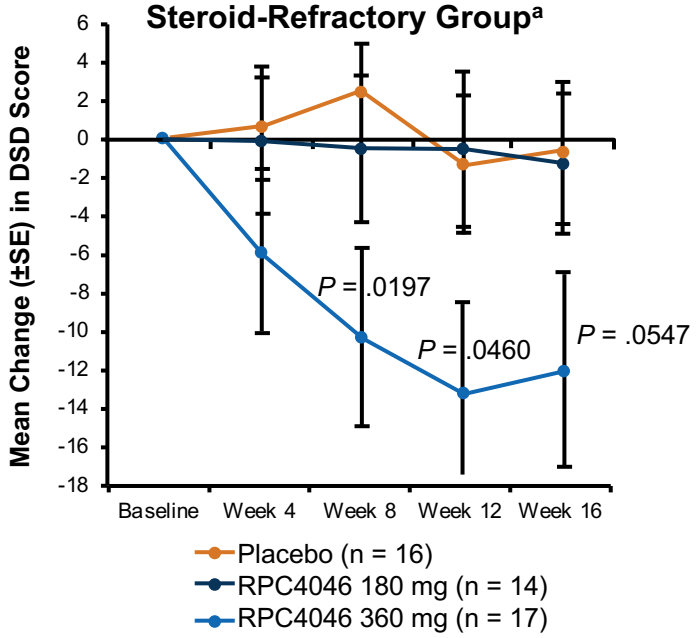




1. Hirano I et al. *Gastroenterology*. 2019;156:592-603.e10.

Cendakimab (RPC4046) Secondary Endpoint: Mean Change in Symptom Score (Daily Symptom Diary)[1]



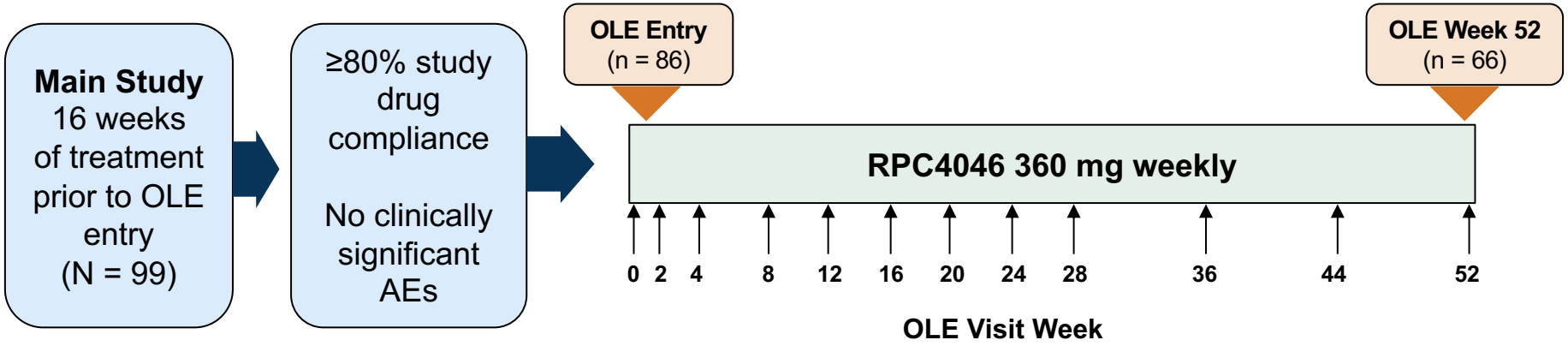


[a] Prespecified subgroup analysis.

1. Hirano I et al. *Gastroenterology*. 2019;156:592-603.e10.

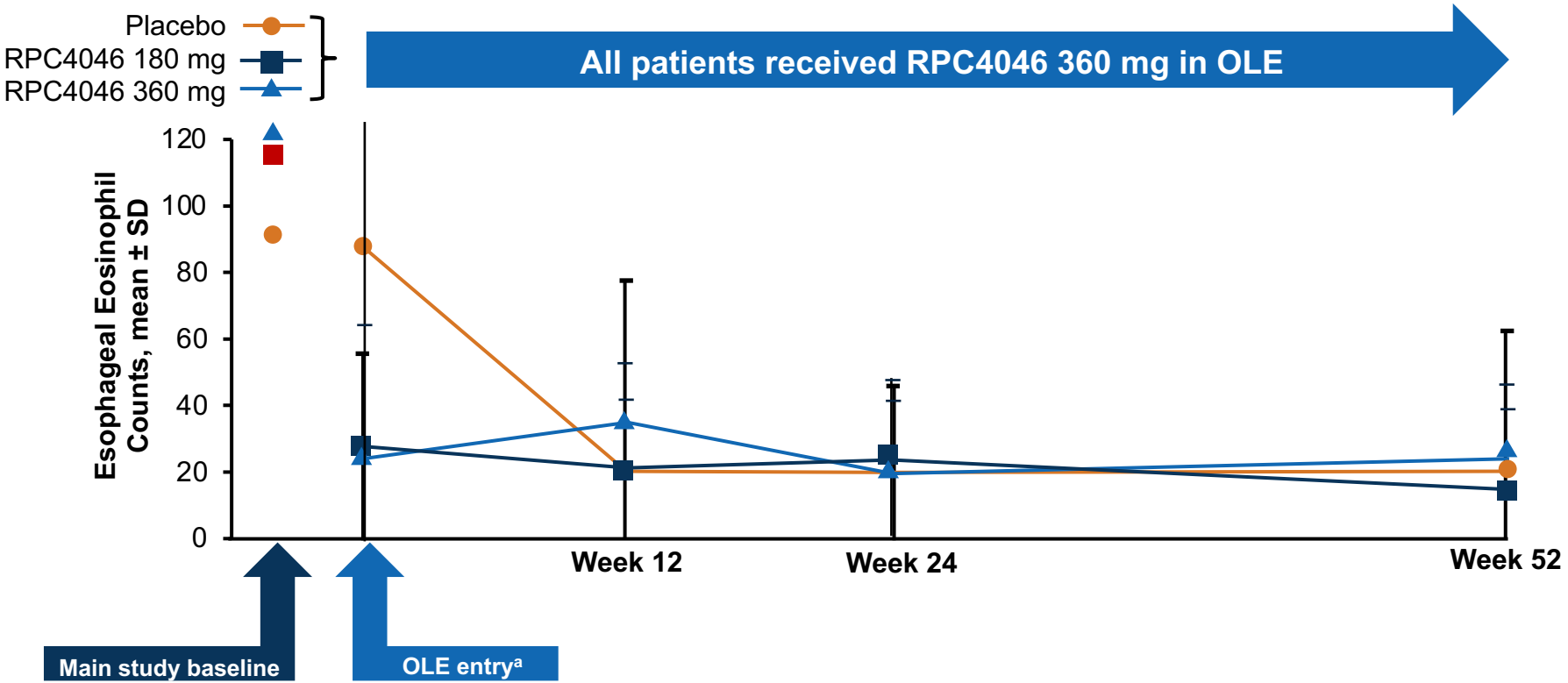
Cendakimab (RPC4046) Open-Label Extension Study[1]

OLE objective: Characterize the long-term effects of RPC4046 in patients with symptomatic EoE on clinical symptoms, endoscopic scores, esophageal histologic findings, and safety for up to 52 weeks



1. Dellon ES et al. *Clin Gastro Hepatol*. 2020;S1542-3565:30348-7.

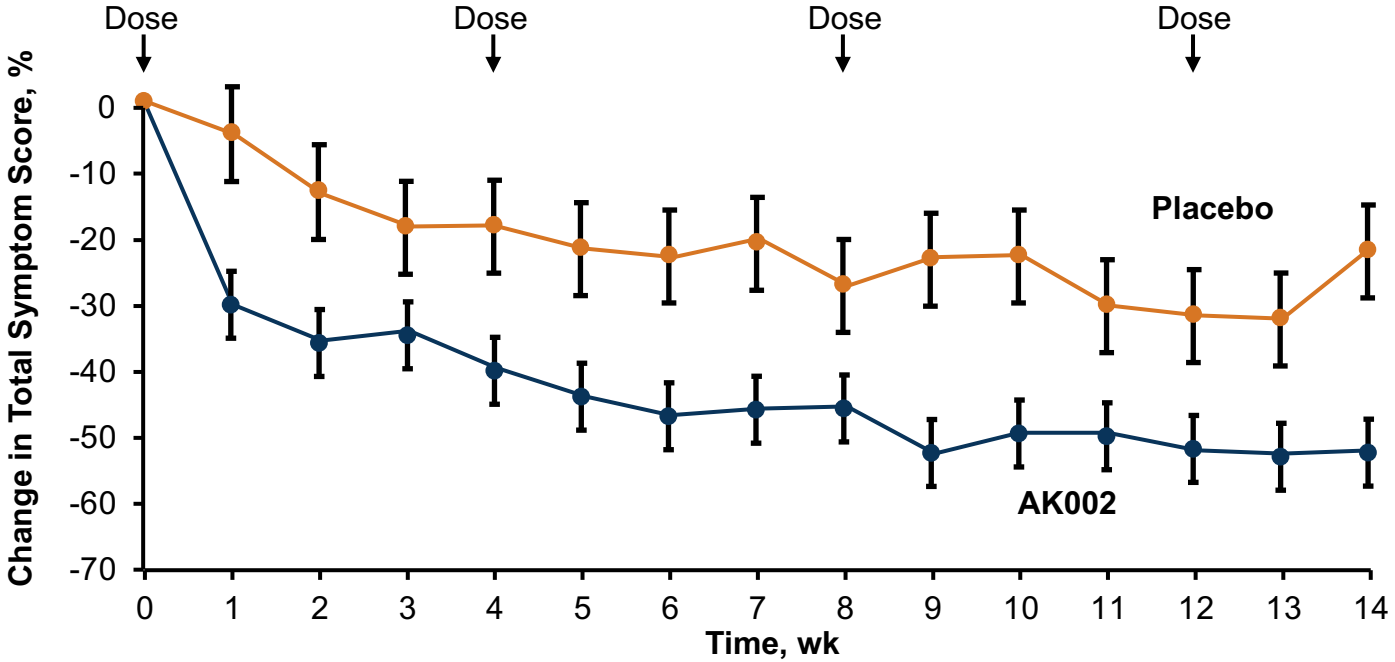
Cendakimab (RPC4046) Open-Label Extension Study: Esophageal Eosinophil Counts[1]



[a] OLE data presented are for observed cases.

1. Dellon ES et al. *Clin Gastro Hepatol*. 2020;S1542-3565:30348-7.

Lirentelimab (AK002), an Anti-Siglec 8 Agent: Phase 2 Results in Adults With Eosinophilic Gastritis, Eosinophilic Duodenitis, or Both[1]



No. of Patients															
Placebo	20	20	19	20	20	19	19	18	18	18	18	19	19	18	18
AK002	39	32	37	37	37	36	38	38	35	37	36	37	36	35	36

1. Dellon ES et al. *N Engl J Med*. 2020;383:1624-1634.

Other Emerging Agents for EoE

- Budesonide oral suspension and orodispersible tab[1,2]
- Fluticasone ODT (phase 3, FLUTE 2)[3]
- Oral etrasimod (phase 2)[4]
- Mepolizumab (anti–IL-5, phase 2)[5]
- Benralizumab (anti–IL-5, FDA Orphan Drug Designation, phase 3)[6]

1. Hirano I et al. *Clin Gastroenterol Hepatol*. 2021;S1542-3565:00456-0. 2. Lucendo AJ et al. *Gastroenterology*. 2019;157:74-86.e15.
3. https://clinicaltrials.gov/ct2/show/NCT04281108. 4. https://clinicaltrials.gov/ct2/show/NCT04682639.
5. https://clinicaltrials.gov/ct2/show/NCT03656380. 6. https://clinicaltrials.gov/ct2/show/NCT04543409.

Clinical Cases Related to EoE

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The Children's Hospital of Philadelphia
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Amal H. Assa'ad, MD
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Cincinnati Children's Hospital
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Kathryn A. Peterson, MD, MSCI
University of Utah
Salt Lake City, Utah

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Patient Case

8-year-old boy with H/O worsening vomiting and epigastric pain

- Symptoms began several years ago
  - Symptoms becoming more frequent
  - No prior treatment
- H/O allergic rhinitis and IgE food allergy to nuts

?

What would you do?

Patient Case

14-year-old white adolescent boy with H/O EoE

- Symptoms began many years ago
  - Treated with topical corticosteroids with resolution of symptoms and eosinophilia
  - Follow-up several years later; the family stopped medication completely
  - Patient asymptomatic
- H/O asthma and eczema

?

What to do?

Remember This as You Return to Your Practices and Patients

Chris A. Liacouras, MD
Division of Gastroenterology, Hepatology and Nutrition
The Children's Hospital of Philadelphia
Professor of Pediatrics
Perelman School of Medicine
University of Pennsylvania
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Overall Treatment Approach

It is easy to …	suspect EoE in patients with dysphagia/food impaction
But we must also …	suspect EoE in patients with a chronic history of vomiting, GERD, epigastric abdominal pain, unusual feeding behavior, or FTT due to feeding problems
In many cases, we should still …	determine if PPI therapy can treat esophageal eosinophilia
Once EoE is diagnosed …	currently treat with dietary restriction or swallowed topical steroids
Symptoms and histology …	do not always correlate
EGD with biopsy …	only current diagnostic tool available to assess histologic esophageal eosinophilia
Biologic treatment …	is on the horizon

Summary

- EoE is a clinicopathologic disease that continues to increase in worldwide incidence and prevalence

- EoE diagnostic criteria have been updated
  - Although a PPI trial is no longer mandatory, physicians need to "think" about process and determine etiology of eosinophilia; it **IS NOT** cookbook medicine
  - Diagnosis is made with the appropriate symptoms in the setting of esophageal eosinophilia (≥15 eos/hpf) that does not have another contributing cause
  - Symptom evaluation should carefully consider that symptoms and eating behaviors are often different in children and adults

- EoE is a progressive disease from inflammation to fibrosis in most, but not all, patients; early diagnosis and ongoing therapy very likely reduces complications

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- **Complete and submit your Post-Test and Evaluation for credit**
- Download the slides and Practice Aids
- Watch the replay of this event in the next 24 hours, to be followed by the online activity in the coming weeks

Have any questions on EoE?
Email us at live@PeerView.com

Thank you for joining us!

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Abbreviations

- ACG: American College of Gastroenterology
- AD: atopic dermatitis
- AGA: American Gastroenterological Association
- AGREE: A Working Group on PPI-REE (proton pump inhibitor–responsive esophageal eosinophilia)
- APT: atopy patch test
- CAPN14: calpain 14
- DPL : dupilumab
- DSG1: desmoglein 1
- DSQ : dysphagia symptom questionnaire
- EGD : esophagogastroduodenoscopy
- EoE: eosinophilic esophagitis
- eos/hpf: eosinophils per high-power field
- ERBIN: Erbb2 interacting protein
- EREFS: Endoscopic Reference Score
- FFED: four-food elimination diet
- FTT: failure to thrive
- HSS: histologic scoring system
- IgE: immunoglobulin E
- IgG: immunoglobulin G
- IL: interleukin
- IL-4: interleukin 4
- IL-5: interleukin 5
- IL-13: interleukin 13
- IL-33: interleukin 33
- IL-4Rα: : interleukin 4 receptor alpha
- IL-13Rα: : interleukin 13 receptor alpha
- JTF: Joint Task Force for Allergy-Immunology Practice Parameters
- LS: least squares

Abbreviations (Cont'd)

- NASPGHAN: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
- ODT: orally disintegrating tablet
- OIT: oral immunotherapy
- OLE: open-label extension
- PBO: placebo
- PPI: proton pump inhibitor
- PPI-REE: proton pump inhibitor–responsive esophageal eosinophilia
- SAE: severe/serious adverse event
- SFED: six-food elimination diet
- SPT: skin prick test
- STAT5: signal transducer and activator of transcription 5
- STAT6:s ignal transducer and activator of transcription 6
- TEAE: treatment-emergent adverse event
- TGFB: transforming growth factor beta
- T_H2: T-helper cell 2
- TIGERS: The International Gastrointestinal Eosinophilic Researchers
- TNF: tumor necrosis factor
- Treg: regulatory T cells
- TSLP: thymic stromal lymphopoietin
- UEG: United European Gastroenterology