

Current and Emerging Therapies for EoE

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Disclosures

- **Astra Zeneca**

- Principal Investigator for Benralizumab clinical trial

- **Bristol Meyers Squibb**

- Principal Investigator for Celgene Cendakimab anti-IL-13 clinical trial

Learning Objectives

- Describe underlying pathophysiology and diagnosis of eosinophilic esophagitis
- Discuss current available dietary and medication treatment options in EoE
- Review new emerging therapies for EoE

Epidemiology

Eosinophilic Esophagitis (EoE)

- Prevalence: 1 per 2,000
- 150,000 cases in US
- Male:Female 3:1
- Burden of disease >\$1 billion annually
- EoE patient with food allergy 68%
 - Reported range 15-68%
- Food allergy patients with EoE 4.72%
 - 570/12,083

EoE: Diagnostic Guideline

EoE is a *clinico-pathological* disease defined by

- Symptoms of esophageal dysfunction
- Esophageal biopsy with eosinophil-predominant inflammation (≥ 15 eos/hpf)
- Disease isolated to the esophagus & other causes excluded (PPI-responsive esophageal eosinophilia)
- Remission of disease with dietary exclusion, topical corticosteroids, or both
- Diagnosed by taking all clinical and pathological information into consideration

New EoE Diagnostic Algorithm

- Clinical presentation suggestive of EoE



EGD with biopsy

- Esophageal eosinophilia >15 eos/hpf (~ 60 eos/mm²)
- Evaluate for non-EoE disorders that cause or potentially contribute to esophageal eosinophilia



- Eosinophilic Esophagitis

PPIs are now used as a therapeutic option rather than a diagnostic criterion

Conditions associated with esophageal eosinophilia

- Eosinophilic esophagitis
- Gastroesophageal reflux disease
- Eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement
- Achalasia and other disorders of esophageal dysmotility
- Hypereosinophilic syndrome
- Celiac Disease
- Crohn's disease with esophageal involvement
- Connective tissue disorders
- Infections (fungal, viral)
- Autoimmune disorders and vasculitides
- Dermatologic conditions with esophageal involvement (ie pemphigus)
- Drug hypersensitivity reactions
- Pill esophagitis
- Stasis esophagitis
- Graft vs host disease
- Mendelian disorders (Marfan Syndrome Type II, Hyper-IgE Syndrome, PTEN Hamartoma Tumor Syndrome, Netherton's Syndrome, Severe Atopy Metabolic Wasting Syndrome)

Eosinophilic Esophagitis

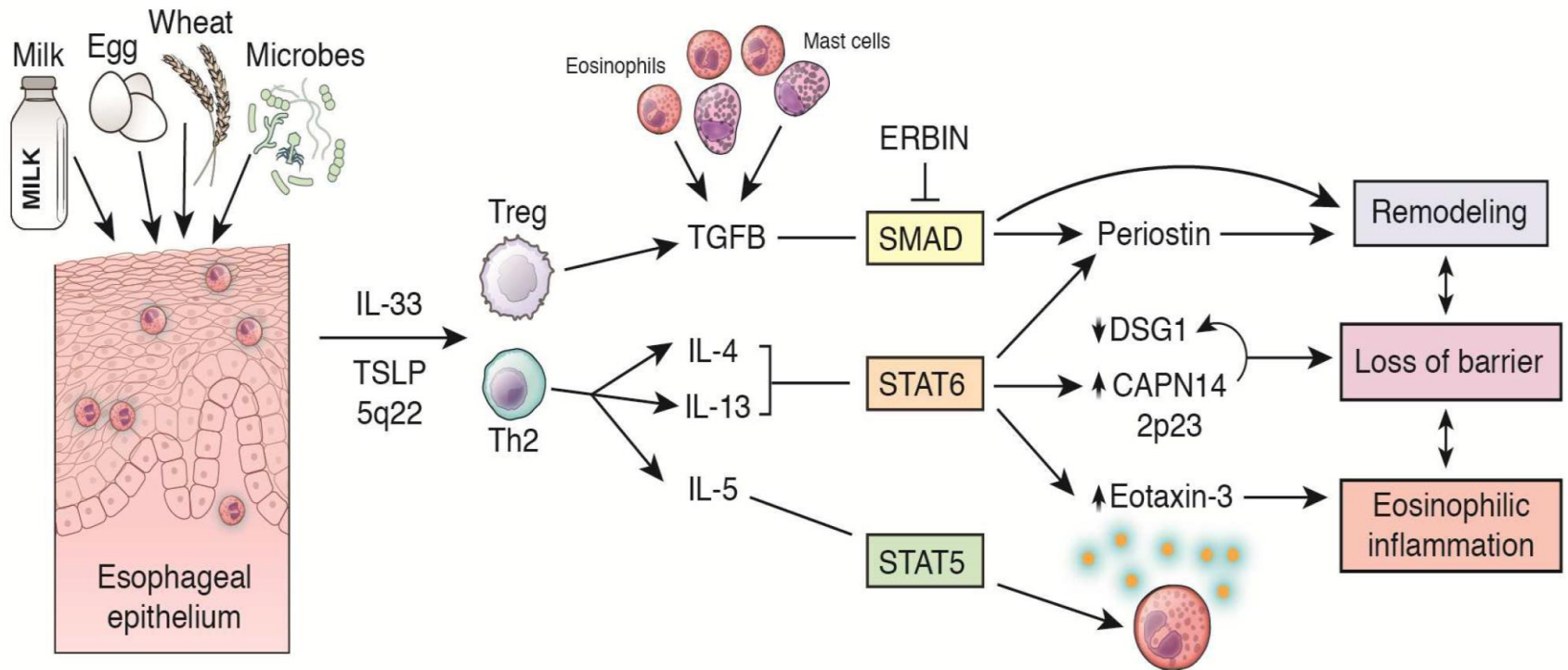
Children vs Adults

Children	Adults
Abdominal Pain	Dysphagia
Nausea/ Vomiting	Food impaction
Failure to thrive	Regurgitation/reflux
Food Aversion	Epigastric to sub-sternal pain
Food Accommodations	Food Accommodations

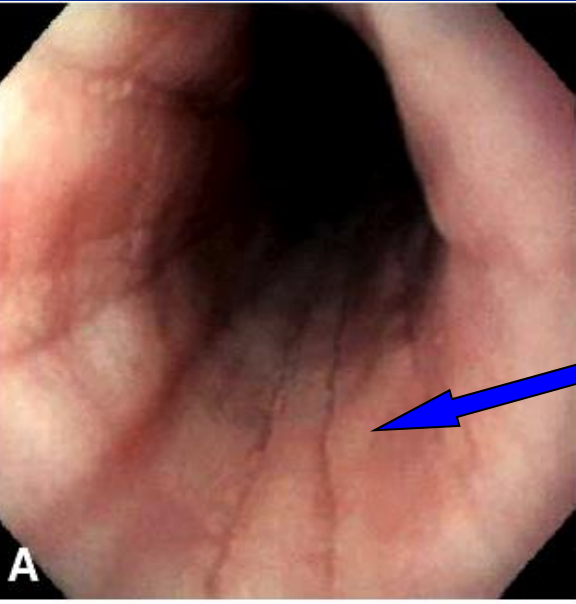
Allergic Disease in EoE Patients

- **IgE-mediated food allergy** **15% - 68%**
- **Allergic rhinitis** **40% - 75%**
- **Asthma** **14% - 70%**
- **Eczema** **4% - 60%**
- **Elevated IgE** **50% - 60%**
- **Peripheral eosinophilia** **40% - 50%**
- **Prominent role for the allergist in management of these patients**

EoE: Pathophysiology



Endoscopic Findings in EoE

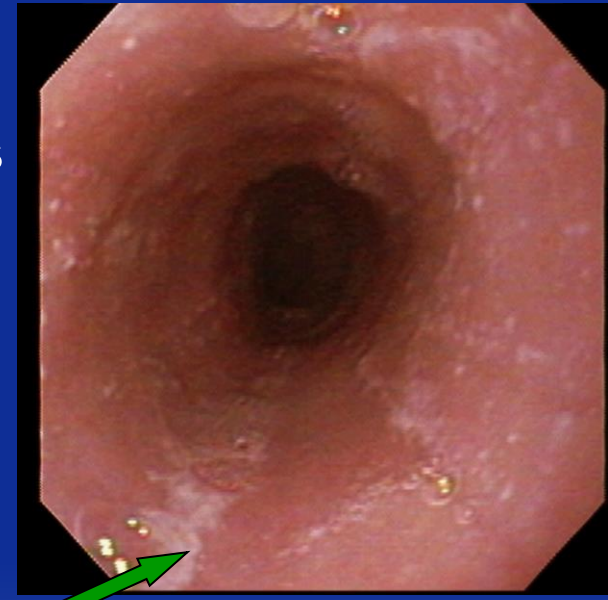


Linear furrowing, vertical lines of the esophageal mucosa

Furrows



White exudates, white specks, nodules, granularity

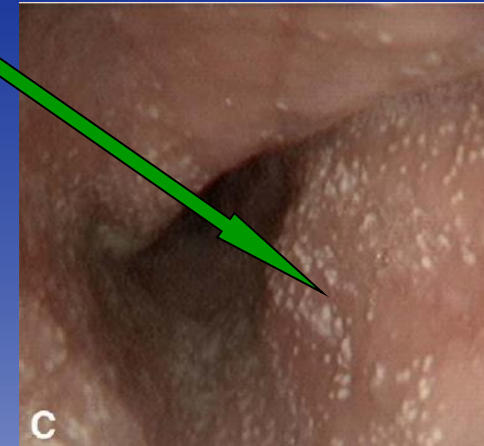
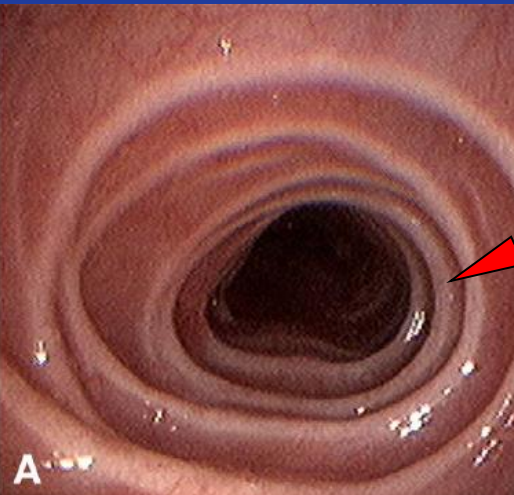


Exudates



Circular rings, transient or fixed

Rings

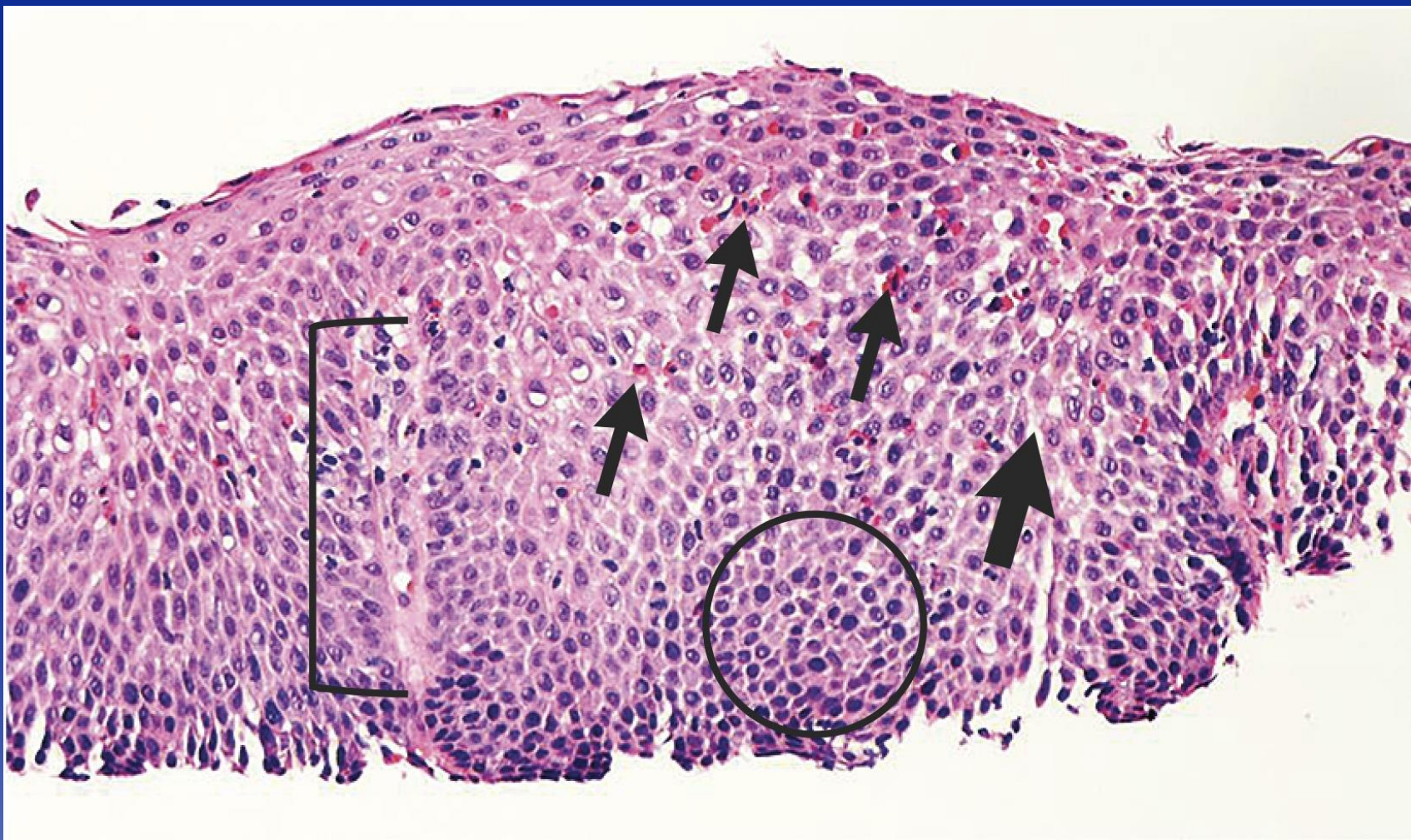


Fox V et al. *Gastrointest Endo* 2003;57:30-36
Desai T et al. *Gastrointest Endo* 2005;61:795
Straumann A et al. *Gastrointest Endo* 2003; 57:407
Gonsalves N, et al. *Gastrointest Endosc* 2006;64:313-9

Endoscopic Findings in EoE

- EREFS and EoEHSS in EoE
- EREFS- Rings, exudates, furrows, edema, stricture
- EoEHSS- 8 parameters of histologic changes characteristic of EoE
 - Peak eosinophils, basal zone hyperplasia >15%, abscess, surface layering, dilated space
- Designed and validated for EoE
 - Mostly being used in research studies

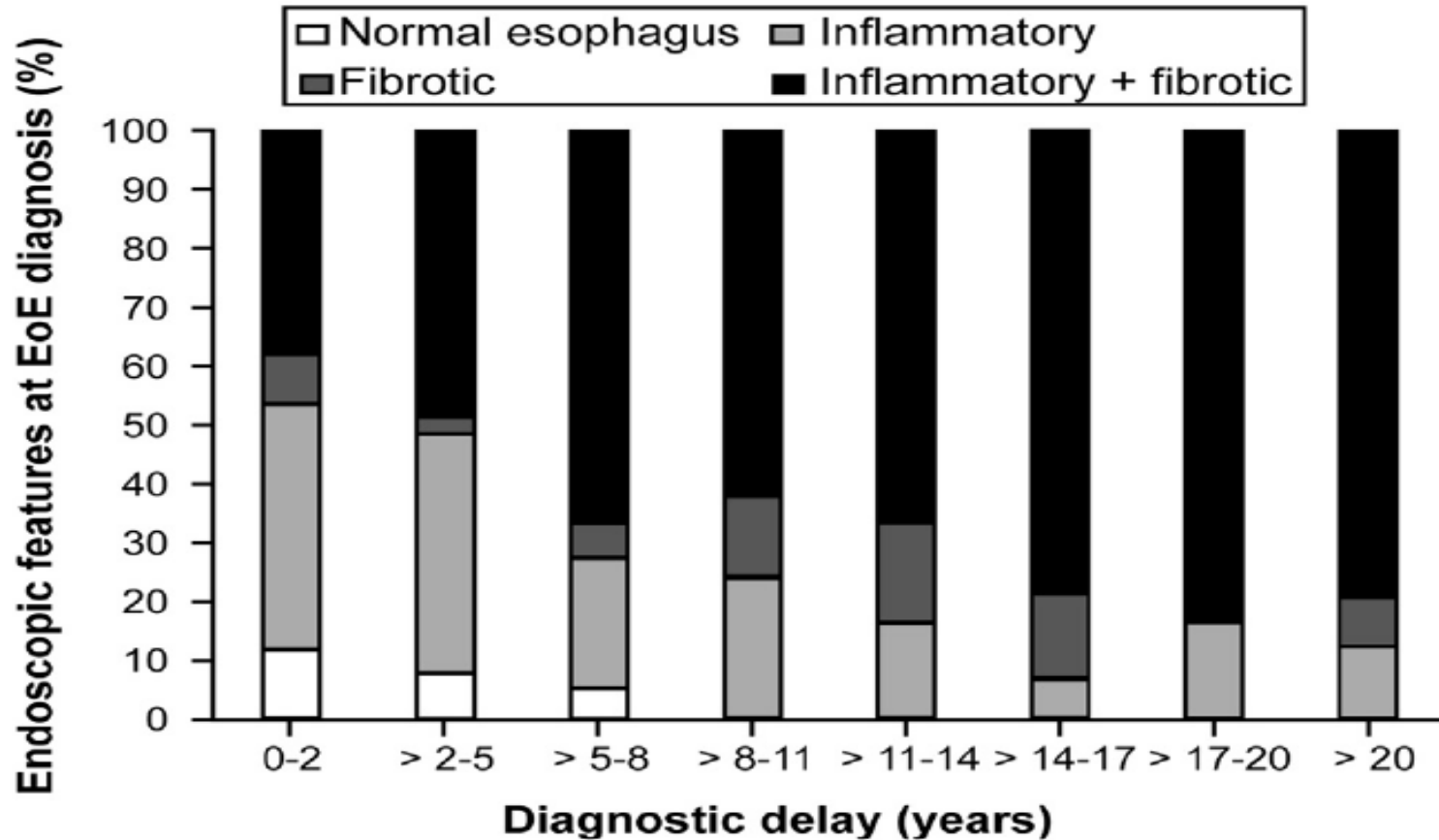
Histologic Characteristics of Eosinophilic Esophagitis



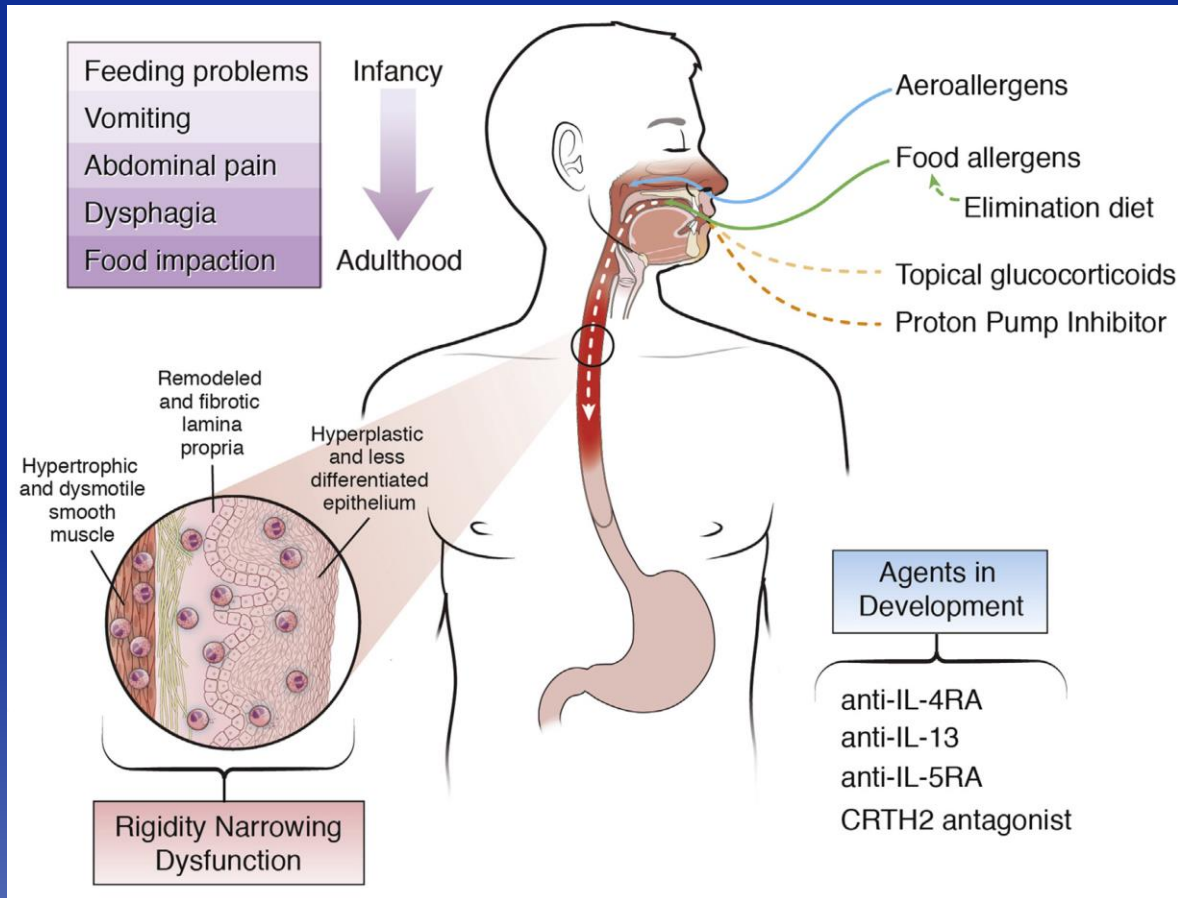
Furuta GT, Katzka DA. N Engl J Med 2015;373:1640-1648

Numerous eosinophils (thin arrows), dilated intercellular spaces (thick arrow), basal zone hyperplasia (circle), papillary elongation (bracket)

EoE Can Lead to Fibrosis



EoE: Treatment Options



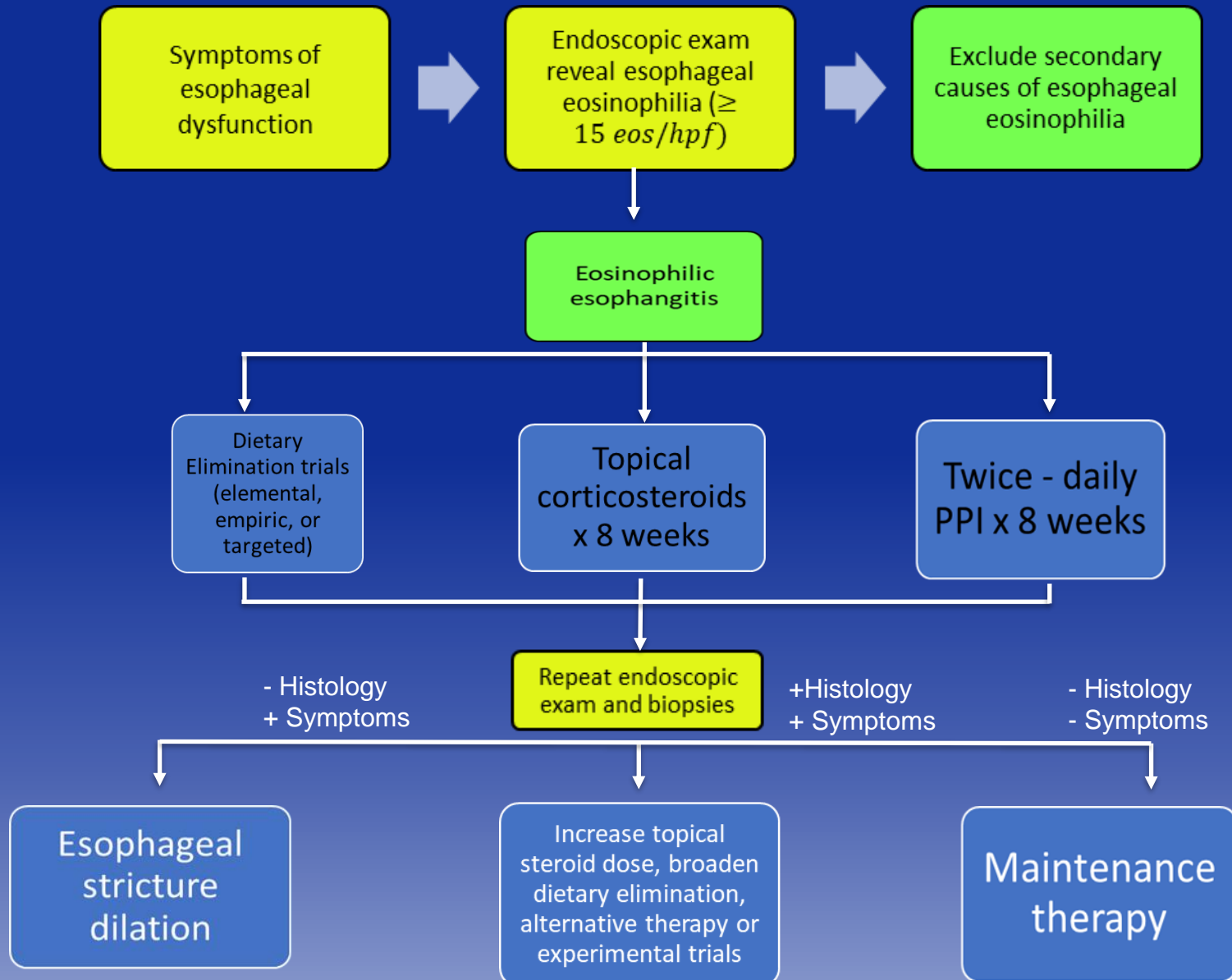
Diet

Dilation

Drugs

No medications have been approved by the US FDA to treat EoE!

Diagnostic/Treatment Algorithm



Current Therapies

Proton Pump Inhibitors (PPIs)

- **PPIs can consider first line therapy for suspected EoE**
- **Treat at least 8 weeks**
 - Dosing: 20-40 mg of selected PPI twice daily or 1 mg/kg/day
 - 36-71% remission of esophageal eosinophils with PPI therapy alone - previously referred to as PPI-responsive EoE (PPI-REE)¹
 - There are no baseline clinical, molecular, endoscopic, or histological features that distinguish PPI-REE from EoE, which led to retirement of this terminology.²
- **Potential benefits with long-term use**
 - Symptom improvement
 - Anti-inflammatory properties of PPIs
 - Promotes healing of esophageal mucosal tissue
 - Reversal of gene expression associated with allergic inflammation
 - Blocks Th2 cytokine-stimulated eotaxin-3 expression
 - Sustained remission in >3/4 patients

¹Vazquez-Elizondo G, et al. Aliment Pharmacol Ther 2013; 38: 1312-9

²Gutierrez-Junquera C, et al. J Pediatr Gastroenterol Nutr 2016; 62: 704-10

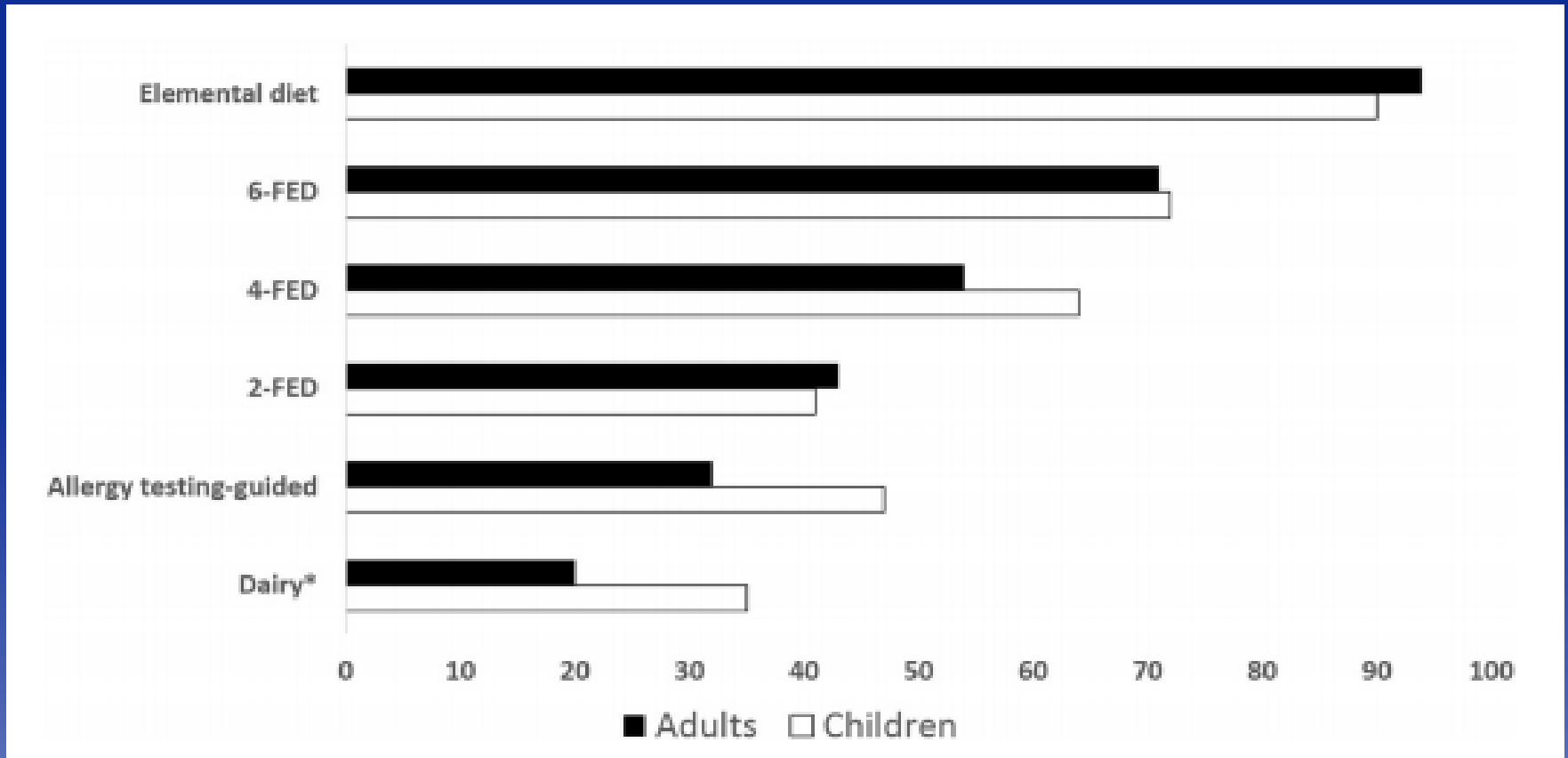
Dietary Avoidance

- Often the reason for GI referral to allergy
- Only non-pharmacologic option
- Discuss different elimination options
 - “step up” approach – less procedures, lower effectiveness
- Start elimination at the beginning of year, avoiding winter holidays
- Inform patients of the need for multiple endoscopies during food introduction
- Challenges
 - compliance, QOL, social activities, nutritional concerns
- Options for failure
 - Expand diet or change therapy?

Options for Identifying Food Trigger

- **Elemental diet** – Clinical improvement and esophageal eosinophilia resolution in 90% of patients – followed by food reintroduction
- **Empiric elimination diet** - Removal of the top food antigens
 - 6FED - Elimination of cow's milk, egg, soy, wheat, nuts (peanuts & tree nuts) and seafood (fish & shellfish)
 - 4FED - Elimination of cow's milk, wheat, egg, soy
 - 2FED – Elimination of cow's milk, wheat
 - Milk elimination – Under investigation
- **Targeted/Directed elimination diet (skin and patch testing)** –
 - May allow less food restriction than empiric. High rates of false test results. Effective in ~40-70% of patients

Histologic Remission Dietary Therapies



Swallowed Topical Steroids (tCS)

- Considered first line by many EoE specialists
- Work through numerous mechanisms
- Efficacy has been proven ~65% (based on 8 RCTs)
- Can restore function and affect tissue remodeling
- Correct deposition crucial to benefit
- Safe/well tolerated
 - Esophageal candidiasis 4-15%
 - Side effects assoc with ICS not typical with tCS
 - Consideration additive effects with tx comorbidities
- Nonadherence appears to be an issue

Topical Steroid Treatments for EoE (off label)

Fluticasone (Flovent): 2 puffs twice a day

1–5 yr, 44 μg

11 yr, 110 μg

12 yr and older, 220 μg

Budesonide (Pulmicort): Respules mixed with Splenda
twice a day

1–5 yr, 0.25 mg/2 ml

6–11 yr, 0.5 mg/2 ml

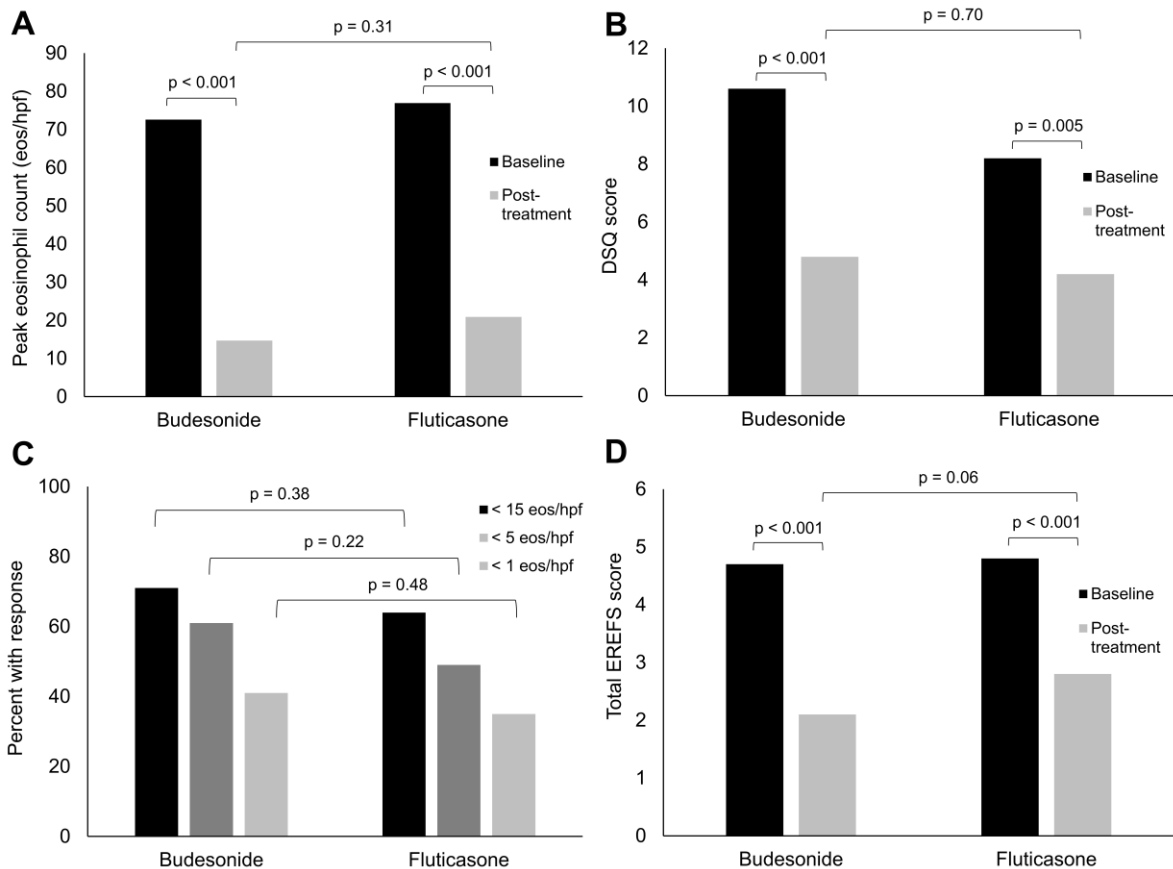
12 yr and older, 1 mg/2 ml

Regularly review technique with patient. No rinsing of mouth, eating
or drinking for 30 minutes after topical steroid administration

Fluticasone vs. Budesonide

Table 4: Adverse events

	Budesonide (n = 65)	Fluticasone (n = 64)
Adverse event (n, %)		
Esophageal candidiasis	8 (12)	10 (16)
Oral candidiasis	2 (3)	1 (2)
Food impaction	0 (0)	1 (2)
Sore throat	0 (0)	2 (3)
Chest pain	0 (0)	1 (2)
Pneumonia	0 (0)	1 (2)
Any adverse event	10 (15)	15 (23)
Serious adverse event	0 (0)	1 (2)



Emerging Therapies

EoE Development Pipeline

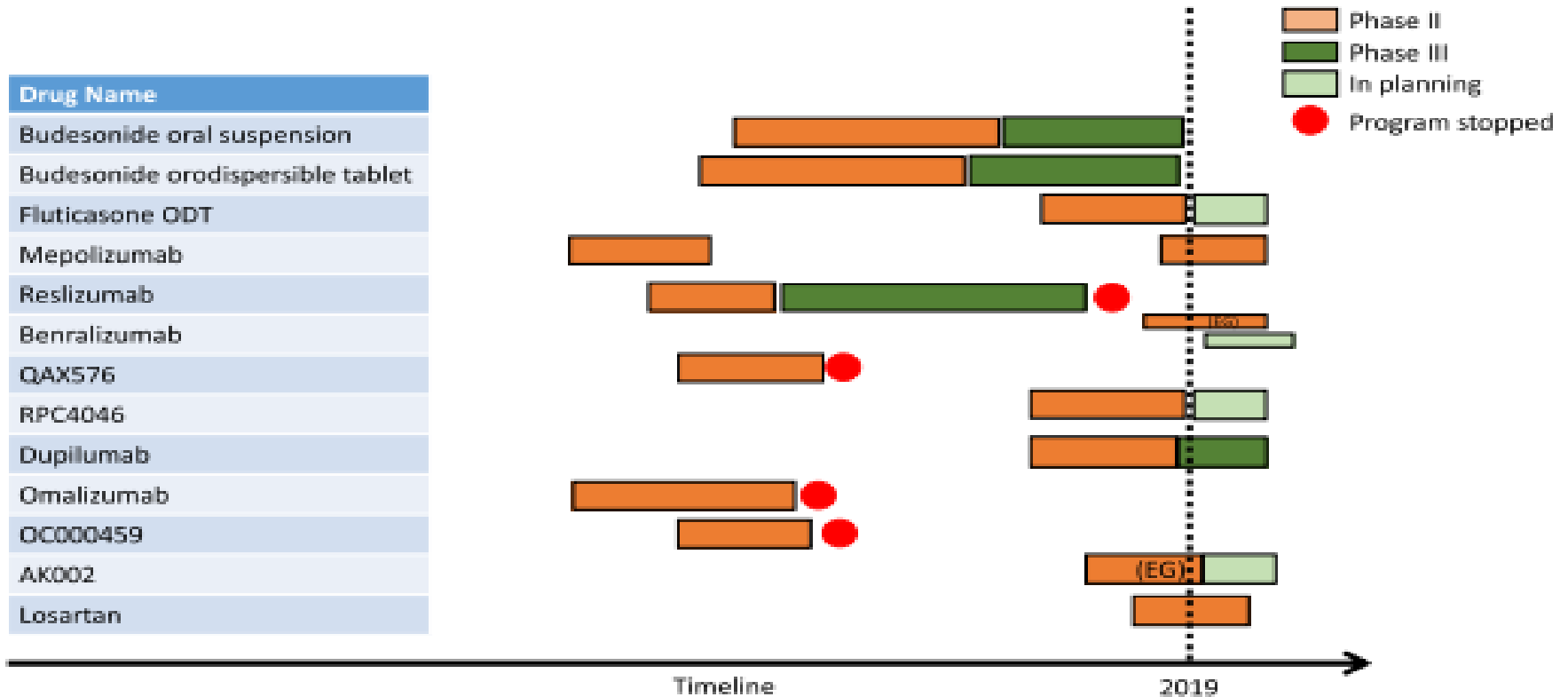


FIG 1. Development pipeline of EoE-specific programs over the last 2 decades with progression from phase II to phase III. *EG*, Eosinophilic gastritis.

New Topical Steroids for EoE

TABLE I. New steroid formulations specifically developed for the treatment of EoE

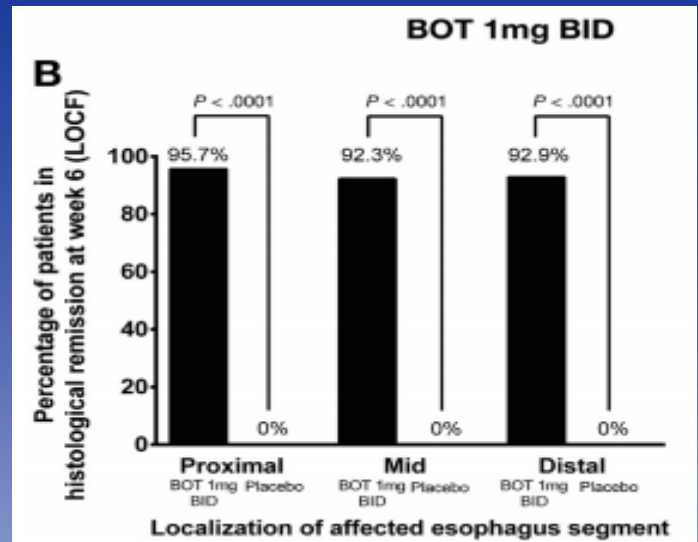
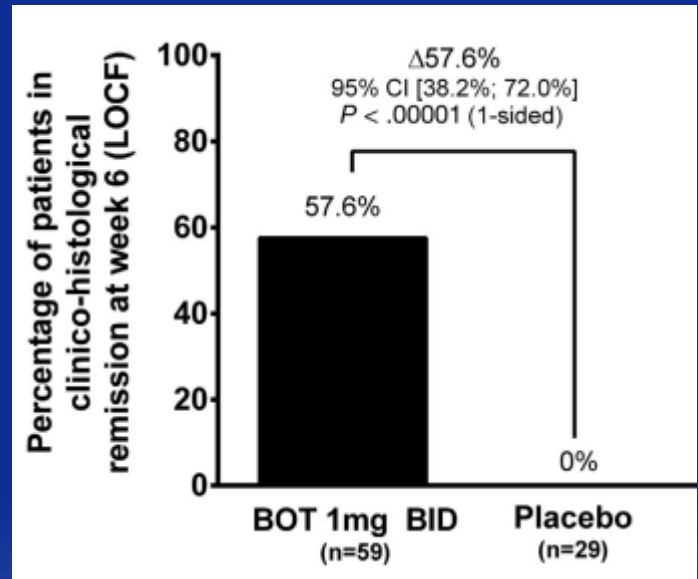
Compound	Studies	Outcome
BET	Short term: Double-blind RCT (n = 88), 6-week treatment course with 1 mg administered twice daily or placebo	Clinicohistologic remission: 58% vs 0% Histologic remission: 93% vs 0%
	Long term: Double-blind RCT (n = 204), 48-week maintenance treatment with 1 or 0.5 mg administered twice daily or placebo	Clinicohistologic remission: 75.0% vs 73.5% vs 4.4% Histologic relapse: 10.3% vs 13.2% vs 89.7%
Budesonide oral suspension	Short term: Double-blind RCT (n = 93), 12-week treatment course with 2 mg administered twice daily or placebo	Change in DSQ score: -14.3 vs -7.5 Histologic response rate: 39% vs 3%
	Long term: Open-label extension study for 24 weeks (2 mg once daily for 12 weeks and optional dose increase to 1.5-2.0 mg administered twice daily for 12 weeks)	Maintenance of remission in 42%, 4% of short-term nonresponders gained response

DSQ, Dysphagia symptom questionnaire; *RCT*, randomized controlled trial.

Fluticasone oral disintegrating tablet (ODT) studied in healthy adults

Budesonide Orodispersible (BOT)

- Multi-center, DBPC, phase 3 trial
- 93 EoE patients, ages 18-75
 - BOT 1 mg BiD
 - Placebo BiD
- 6 weeks treatment



Approved by the EMA
Jorveza age 18+

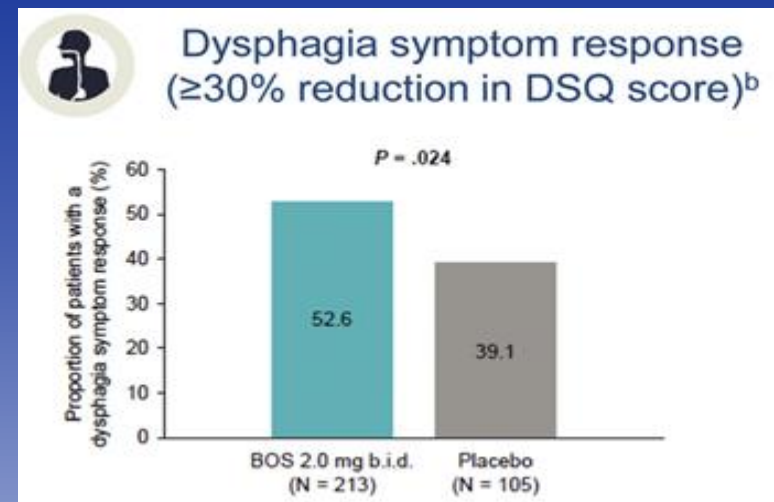
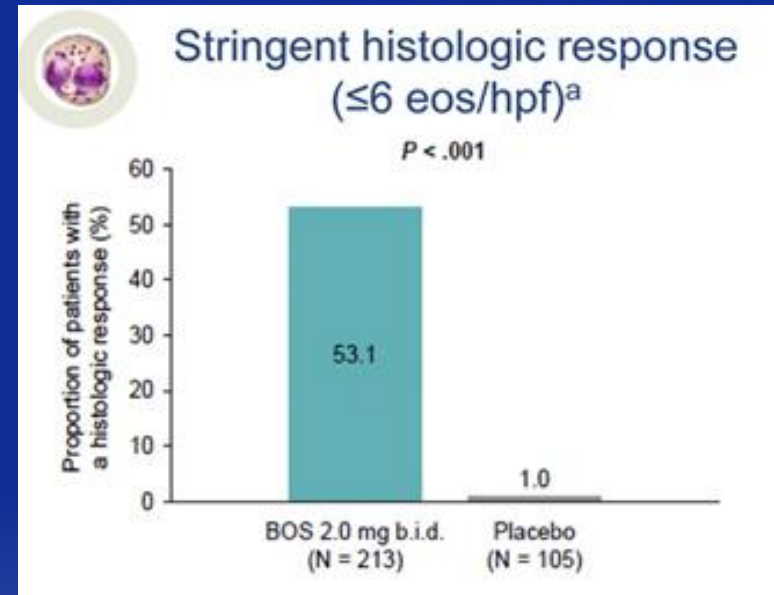
Budesonide Oral Suspension (BOS)

Muco-adherent topical corticosteroid liquid formulation, with standardized viscosity and concentration for EOE

- **Two phase 2, multicenter, randomized PC trials**
 - MPI 101–01: 71 patients 2-18 years old
 - Treatment with medium or high dose BOS significantly improved histologic parameters in patients with EoE (n =36) vs placebo (n = 18)
 - MPI 101–06: 93 patients 11-40 years old
 - Treatment with BOS (2 mg twice daily) for 12 weeks significantly improved symptomatic, endoscopic and histologic parameters in patients with a EOE (n = 49) versus placebo (n = 38)
- **Phase 3, randomized, multicenter 12 week DBPC trial**
 - 318 Patients age 11-55 randomized 2:1 BOS 2 mg twice daily vs placebo
 - Met both coprimary efficacy endpoints (symptom and histologic response) and the key secondary endpoint (change in DSQ score)

Budesonide Oral Suspension (BOS)

- Multicenter, DBPC, phase 3, 12 week trial
- 318 patients, age 11-55
- Randomized 2:1
 - BOS 2 mg BOD
 - Placebo BiD



Takeda Pharma presentation data on file
Hirano et al presented ACG 2019

Anti IL-5

- **Mepolizumab**

- Decreased eosinophilia but only minor symptomatic improvement. Two studies N=11 adults, N=59 children
- Needs further study

- **Reslizumab**

- Reduced eosinophilia without effect on symptoms N=227 children and adolescents
- 6 patients continued OLE, 4 compassionate use-9 yrs
- Histologic response and symptomatic improvement
- No control group

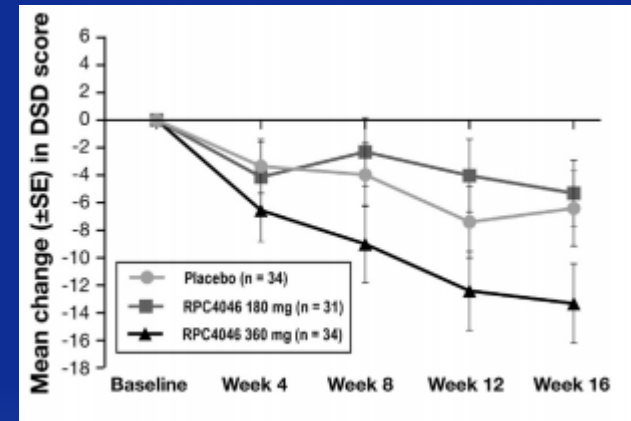
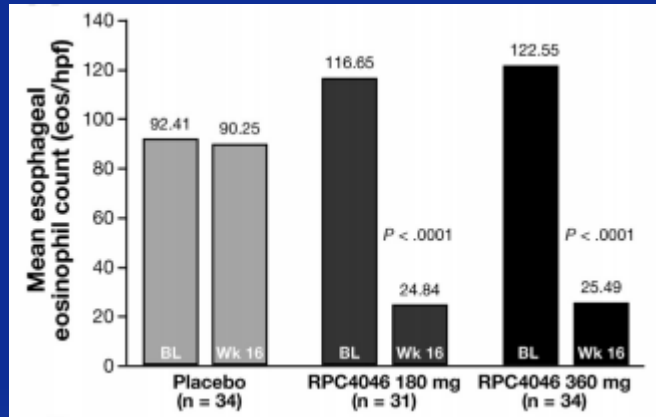
Benralizumab

Anti-IL-5R mAb

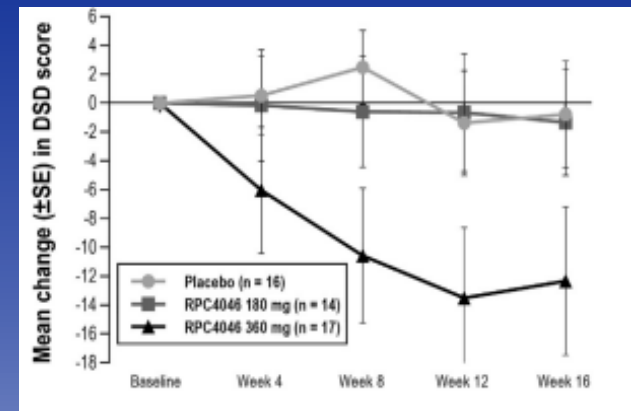
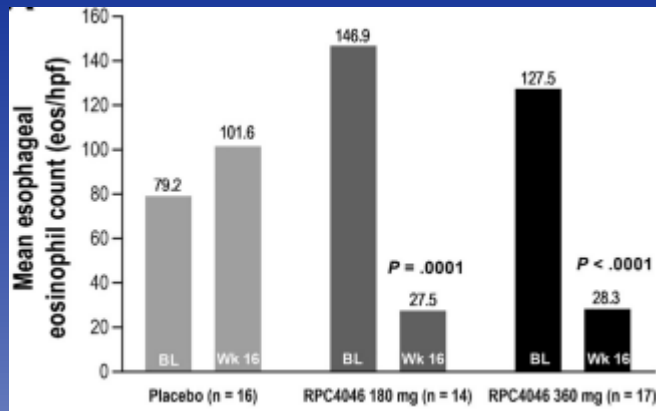
- No clinical trial data available
- Published case reports esophageal eosinophilia
 - Near complete eradication esophageal eosinophilia and symptomatic improvement
- Messina (Ongoing Phase III Clinical Study) EoE
 - Ages 12-65 DBPC 24 wk, Open-label 28 wk
 - Primary endpoints:
 - Proportion pts Intraepithelial eosinophil ct \leq 6/hpf
 - Change from baseline DSQ week 24
 - Number of secondary endpoints

Anti-IL-13 mAb cendakimab (prev RPC4046)

Phase 2 trial
All patients
N=99 adults
1:1:1 16 weeks



Steroid
refractory
N=47



Anti-IL-13 mAb cendakimab (prev RPC4046)

- **First Biologic study to look at EREFS and EoEHSS in EoE**
 - **Designed and validated for EoE**
- **Phase 3 trial age 12+ currently enrolling**
 - **CC-93538**
- **Another anti-IL-13 QAX576- did not meet primary endpoint N=25 adults but some positive trends were noted.**

EREFs- Rings, exudates, furrows, edema, stricture
EoEHSS- 8 parameters of histologic changes characteristic of EoE

Dupilumab

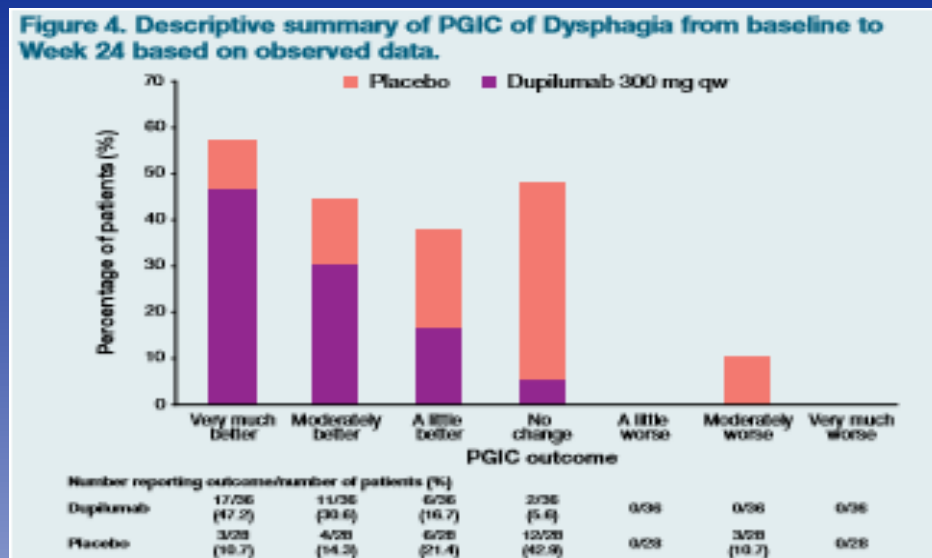
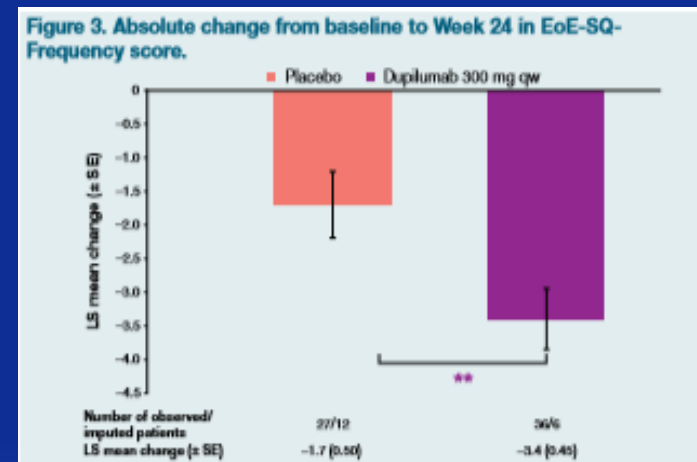
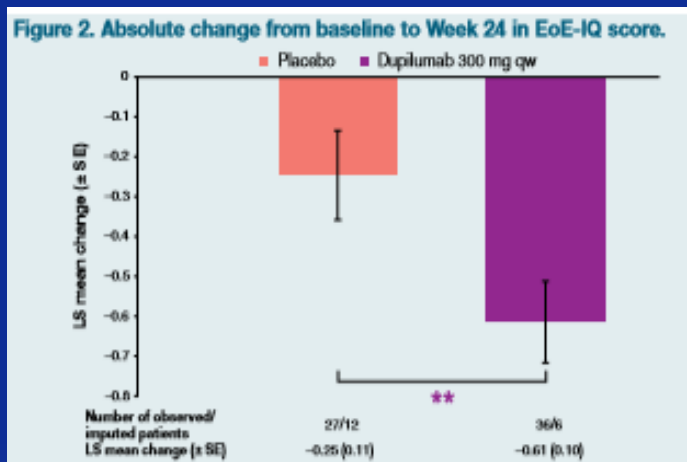
- Phase 2 Study
 - N= 47 adults, multicenter DBPC
 - Dupilumab 300mg wkly after 600mg load dose or placebo
 - Primary endpt significant improvement (SDI PRO)
 - Key secondary endpts
 - Decrease intraepithelial eosinophils 92.9% vs 14.2% placebo
 - Greater improvement EoE-EREFS score vs placebo
- Phase 3 LIBERTY EoE TREET study
 - N= 81 Adult and adolescents, DBPC 24 weeks
 - Primary endpt prop pts achieving peak eosinophil ct ≤ 6 /hpf
 - Dysphagia Symptom Questionnaire Score chg from baseline

SDI PRO Straumann Dysphagia Instrument Score
EoE-EREFS Eosinophilic –Endoscopic Reference
Score

Hirano et al Gastroenterology 2019
Data on file Regeneron Pharmaceuticals

Dupilumab Improves Health-Related Quality of Life and Reduces Symptoms Burden in Patients with Eosinophilic Esophagitis: Results from Part A of a Randomized, Placebo-Controlled, Three-Part, Phase 3 Study

N=81
 Age 12+
 PPI non-responders
 Randomized 1:1
 24 week treatment
 period



Other Therapies

- Anti-IgE Omalizumab
 - Open label trial. N=15
 - Clinicohistologic remission in 33%
 - Randomized control trial N=30
 - no significant improvement
- Anti-TNF Infliximab
 - Open label N=3 no benefit
- CRTH2 antagonist OC000459
 - Randomized placebo controlled N=26
 - Reduced esophageal eosinophilia by 36%
 - Patient reported outcomes did not differ
 - No effect on EGD

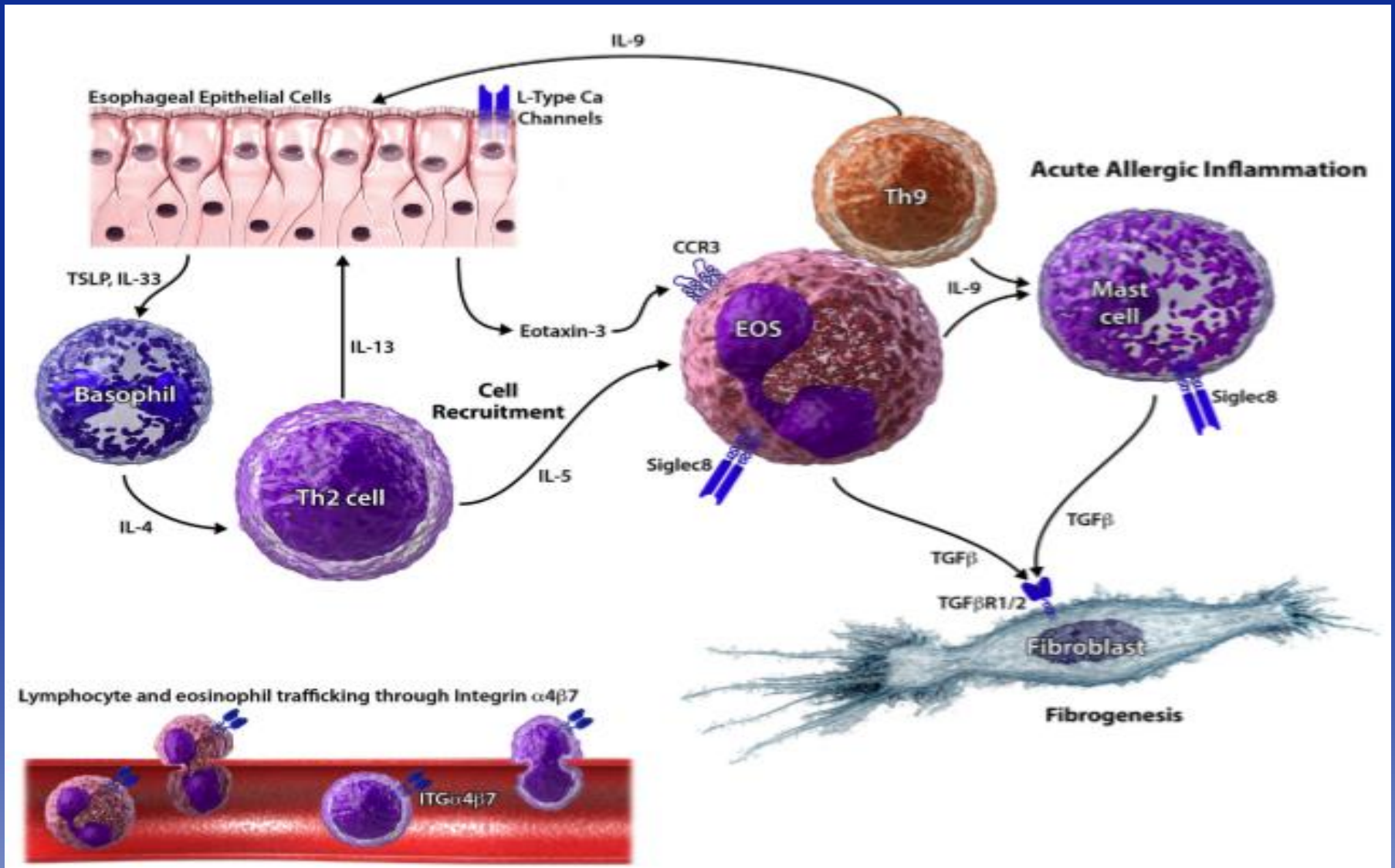
Potential Targets

- Sialic acid-binding immunoglobulin-like 8 (Siglec-8)
 - Selectively expressed on eosinophils, mast cells and basophils
 - Key role in apoptosis
 - Anti-Siglec-8 phase 2 trial eosinophilic gastroenteritis
 - Depletion of eosinophils and symptom improvement
 - Efficacy in EoE not available
- Calcium channel blocker
 - Verapamil attenuates IL-4-induced eotaxin expression

Future Potential Targets

- Integrin alpha4beta7
- TSLP
- TGF-beta
- Eotaxin receptor anti-CCR3
- IL-9, IL-15, IL-33

Future Targets



Summary

- PPI still first line medical treatment
- Dietary therapy works and is preferred non-pharmacologic treatment but tedious process and not all patients interested
- Topical steroids proven efficacy
- No FDA approved products but getting closer
- Large unmet need for new therapies
- Numerous ongoing clinical trials
- Shared decision making is key

Education, advocacy, and/or research support resources:

- American Academy of Allergy, Asthma, and Immunology: www.aaaai.org
- American Partnership for Eosinophilic Disorders: www.apfed.org
- Campaign Urging Research for Eosinophilic Disorders: www.curedfoundation.org
- Children's Digestive Health and Nutrition Foundation: <https://naspghan.org/naspghan-foundation/>
- Food Allergy & Anaphylaxis Network: www.foodallergy.org
- North American Society of Pediatric Gastroenterology and Nutrition: www.naspghan.org
- Registry for Eosinophilic Gastrointestinal Disorders: <https://www.rarediseasesnetwork.org/cms/cegir>