



ADVANCING GI PATIENT CARE

APRIL 28–30, 2023
Frisco, Texas

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Mallinckrodt Pharmaceuticals, Pfizer Inc., and Salix Pharmaceuticals.



The background of the slide is an aerial photograph of a city skyline, likely Philadelphia, with various skyscrapers and buildings. The image is overlaid with large, semi-transparent blue geometric shapes: a large triangle on the left side and several diagonal lines crossing the bottom and right portions of the frame. The text is centered in the upper half of the image.

Eosinophilic Esophagitis

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Disclosures

- Consultant:
 - Adare/Ellodi
 - Allakos
 - Bristol Myers Squibb/Celgene
 - Lucid
 - Nexstone
 - Phathom
 - Regeneron/Sanofi
 - Shire/Takeda
 - Upstream Bio
- Research Support:
 - Adare/Ellodi
 - Allakos
 - Arena/Pfizer
 - Bristol Myers Squibb/Celgene
 - Lucid
 - Nexteos
 - Regeneron/Sanofi
 - Shire/Takeda

Learning Objectives

- What are the goals of therapy in EoE?
- What are treatment options in 2023?
- How do I assess response to therapy?
- What are the data for chronic therapy?
- What new treatments are under study
- What about refractory EoE?

Learning Objectives

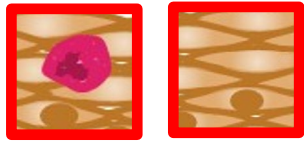
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EoE: Treat to Target



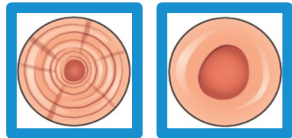
Symptoms

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)

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Initial Choice of EoE Therapy: Variables to Consider

- Efficacy & adverse events
- Patient preference
- Disease severity
- Insurance coverage
- Dietary resources
- *Shared decision making guides treatment decisions*

Eosinophilic Esophagitis Management

- Diet
- Drugs
 - PPI
 - Topical steroids
- Dilation
- Dupilumab
- Investigational agents
 - Novel steroid delivery platforms
 - Biologics

AGA & Joint Task Force Guideline: Dietary Treatment of EoE

Treatment	Number of studies	Overall Effect
Elemental diet	6	94%
SFED	10	68%
Allergy directed elimination	12	52%

Efficacy: < 15 eosinophils/hpf

RCT of 1-FED Vs 6-FED for EoE

	1-FED (N=67)	6-FED (N=62)	P-value
< 15 eos/hpf	23 (34%)	25 (40%)	0.58
	Subsequent 6-FED	Subsequent fluticasone 880 <i>ug</i> bid	
< 15 eos/hpf	9/21 (43%)	9/11 (82%)	

AGA & Joint Task Force Guideline: PPI Therapy for EoE

Treatment	Number of Studies	Number of Patients	Overall Effect	I ²
PPI	23	1051	42%	81%

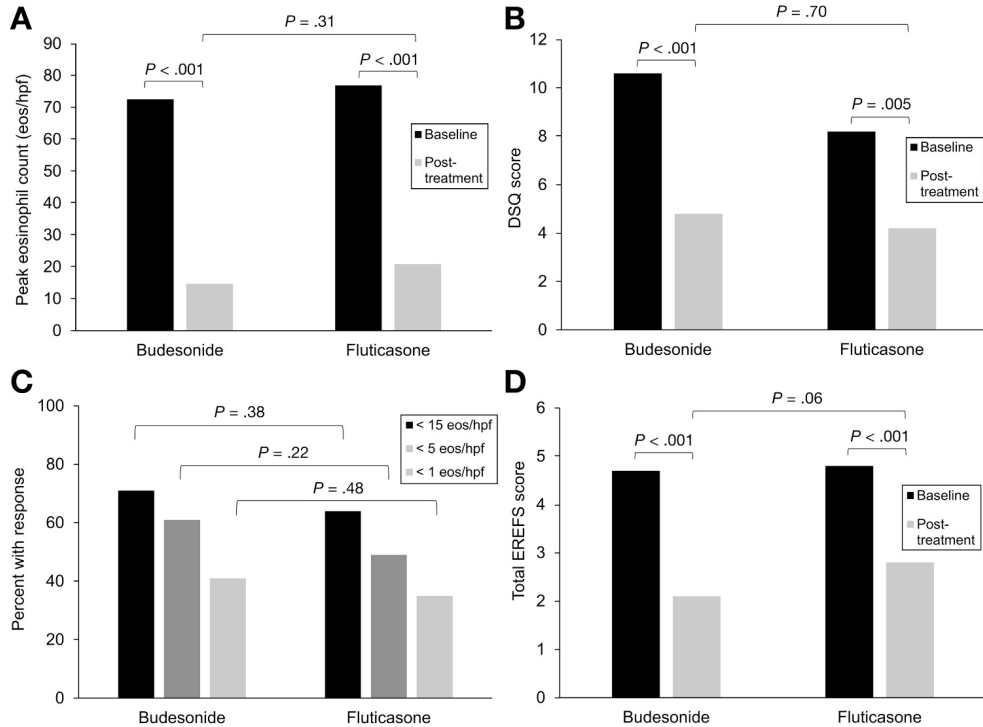
Efficacy: < 15 eosinophils/hpf

AGA & Joint Task Force Guideline: Topical Corticosteroid Therapy for EoE

Treatment	Number of Studies (All RCT)	Number of Patients	Overall Effect	I ²
Topical steroids	8	437	65%	77%

Efficacy: < 15 eosinophils/hpf

8 Week RCT of Budesonide (1 mg BID) Vs. Fluticasone (880 ug BID) For EoE



Histologic response (< 15 eos/hpf)
Budesonide: 71%
Fluticasone: 64%

AGA & Joint Task Force Guideline: Topical Corticosteroid Therapy for EoE

- No increased risk of AEs when compared to placebo in short term studies
- Scattered reports:
 - Adrenal suppression
 - Local fungal/viral infections

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dupilumab in Adults and Adolescents with Eosinophilic Esophagitis

E.S. Dellon, M.E. Rothenberg, M.H. Collins, I. Hirano, M. Chehade, A.J. Bredenoord, A.J. Lucendo, J.M. Spergel, S. Aceves, X. Sun, M.P. Kosloski, M.A. Kamal, J.D. Hamilton, B. Beazley, E. McCann, K. Patel, L.P. Mannent, E. Laws, B. Akinlade, N. Amin, W.K. Lim, M.F. Wipperman, M. Ruddy, N. Patel, D.R. Weinreich, G.D. Yancopoulos, B. Shumel, J. Maloney, A. Giannelou, and A. Shabbir

Dupilumab Inhibits IL-4 & IL-13 Signaling

1

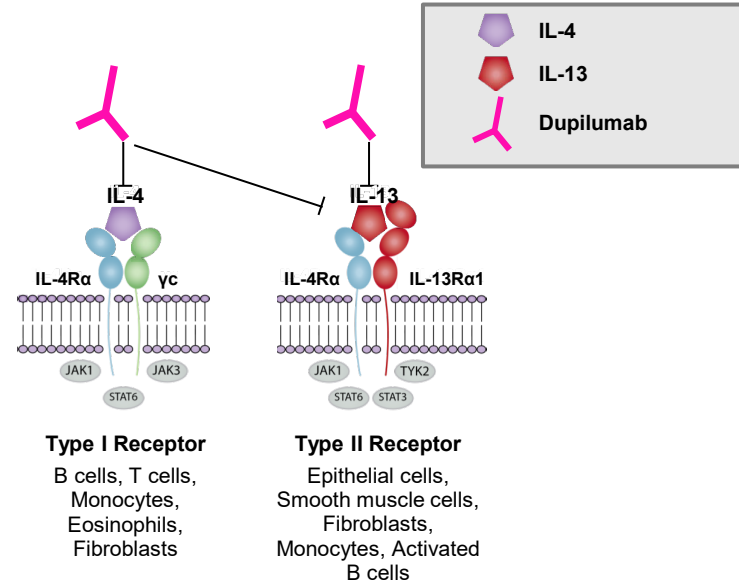
IL-4 and IL-13 bind to a shared subunit, IL-4R α

2

Dupilumab, a human monoclonal IgG4 antibody, binds to IL-4R α , blocking both IL-4 and IL-13 signalling pathway

3

IL-4 and IL-13 pathways have unique and overlapping function

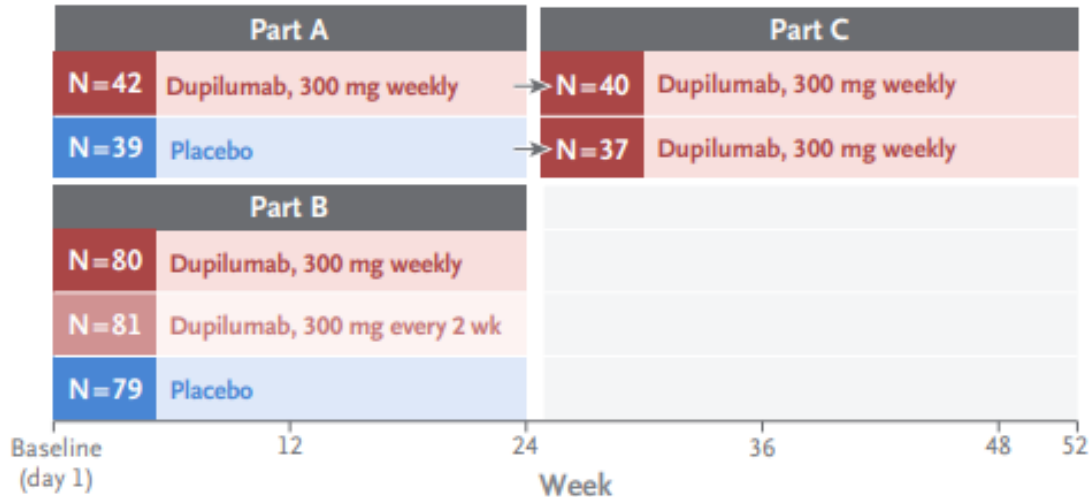


yc, gamma chain; IL-4R α , interleukin-4 receptor alpha; IL-13R α 1, interleukin-13 receptor alpha 1; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase.

From Gandhi NA et al. *Nat Rev Drug Discov.* 2016;15:35–50.

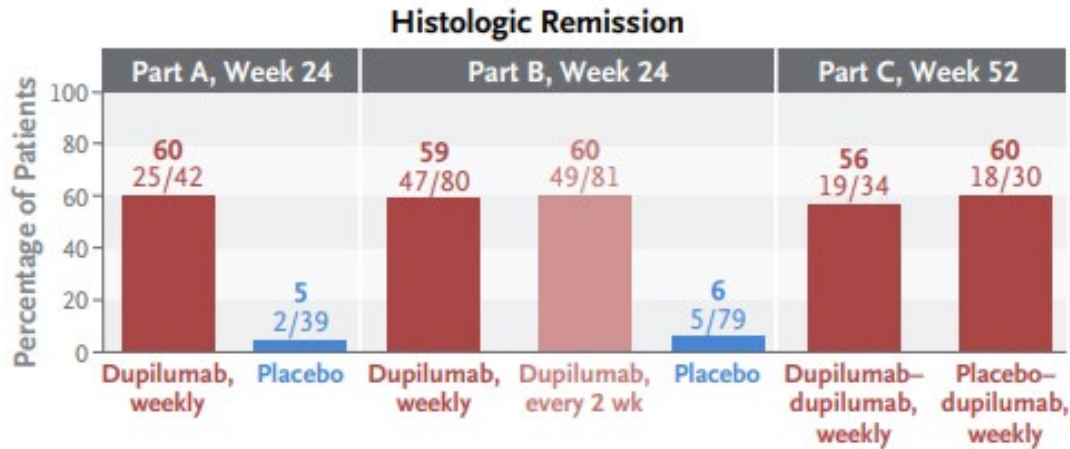
Dupilumab in EoE: Trial Design

Phase 3 Trial Design (all doses delivered subcutaneously)



- ≥ 12 yrs
- ≥ 15 eos/hpf
- Failure of high dose PPIs
- DSQ ≥ 10

Dupilumab in EoE: Histologic Remission (≤ 6 eos/hpf)



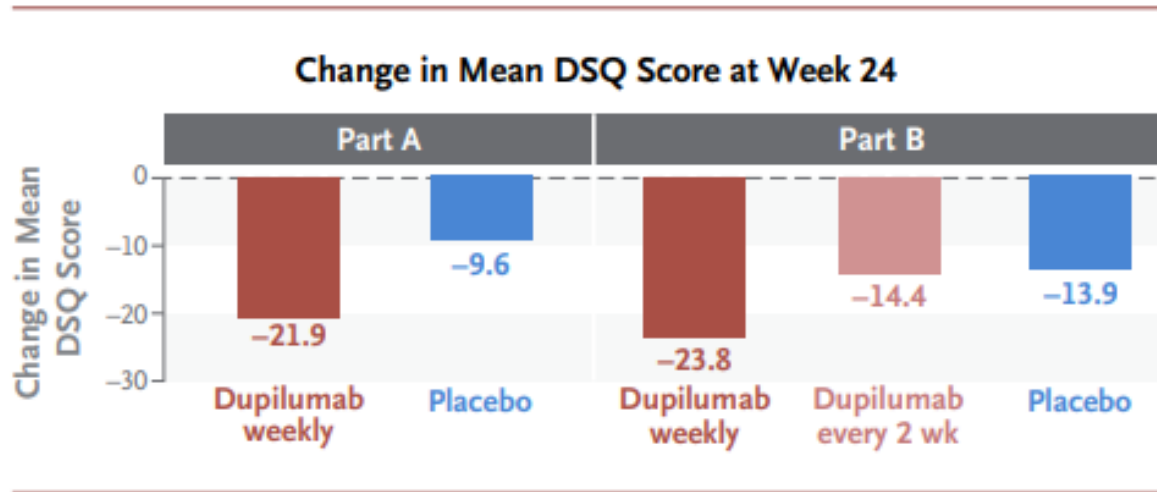
< 15 eos/hpf: delta vs placebo

A: 58%

B: 75% [weekly]

72% [every 2 weeks]

Dupilumab in EoE: Symptom Response



Dupilumab in EoE: Adverse Events

Incidence of Adverse Events at Week 24

Adverse Event	Part A		Part B		
	Dupilumab, weekly (N=42)	Placebo (N=39)	Dupilumab, weekly (N=80)	Dupilumab, every 2 wk (N=81)	Placebo (N=78)
	<i>no. of patients (%)</i>				
Death	0	0	0	0	0
Any adverse event	36 (86)	32 (82)	67 (84)	63 (78)	55 (71)
Serious adverse event	2 (5)	0	5 (6)	1 (1)	1 (1)

Injection site reaction: 17-22%
Injection site erythema: 7-22%
Nasopharyngitis: 2-12%

Clinical Guidance for Use of Dupilumab as First Line Therapy

- Multiple comorbid atopic conditions
 - Moderate, persistent or difficult to control asthma
 - Need for maintenance steroids
 - Moderate, persistent or difficult to atopic dermatitis
 - Need for maintenance medium strength topical steroids
 - Difficult to control chronic sinusitis with nasal polyps
- Patients with strong preference to avoid dietary restrictions or topical steroids

Clinical Guidance for Use of Dupilumab as Step Up Therapy

- Difficult to treat EoE
- Frequent use of rescue therapy
- Severe dietary restriction
- Clinically significant strictures or narrow caliber esophagus
 - No superiority data

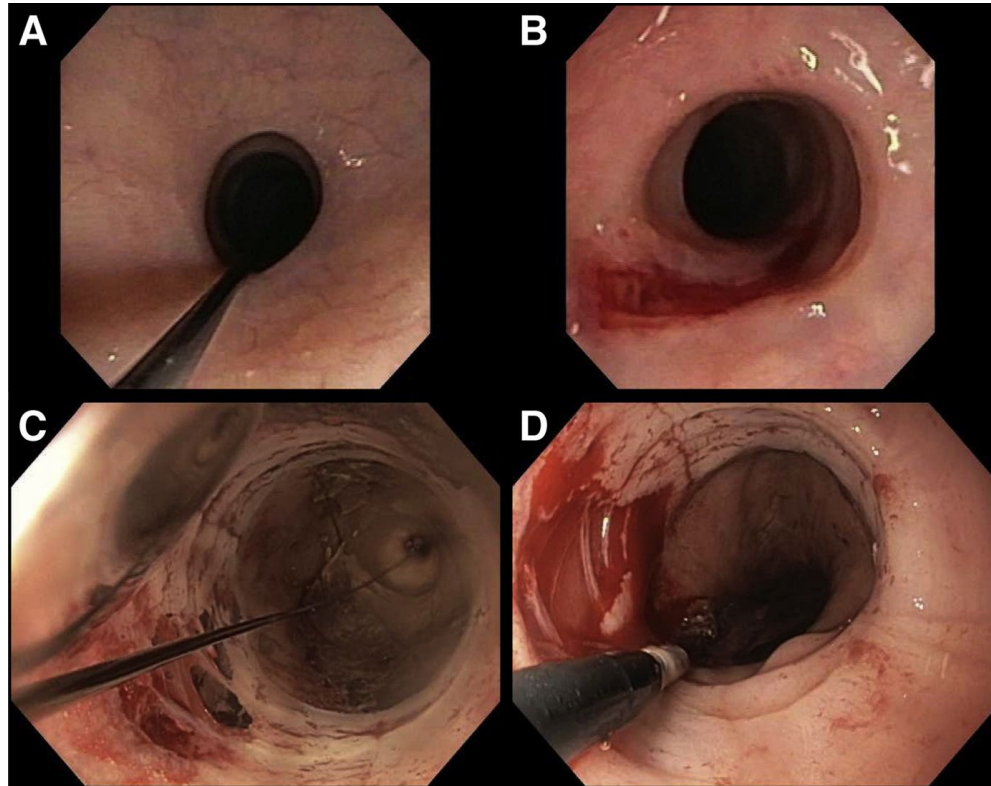
Clinical Guidance for Use of Dupilumab as Therapy: Refractory Disease

- Continued symptoms-beware!
- Persistent esophageal inflammation
- AE with current therapy
 - Think multiple topical steroid targets
- Intolerance to current therapy
- Non-adherence to current therapy

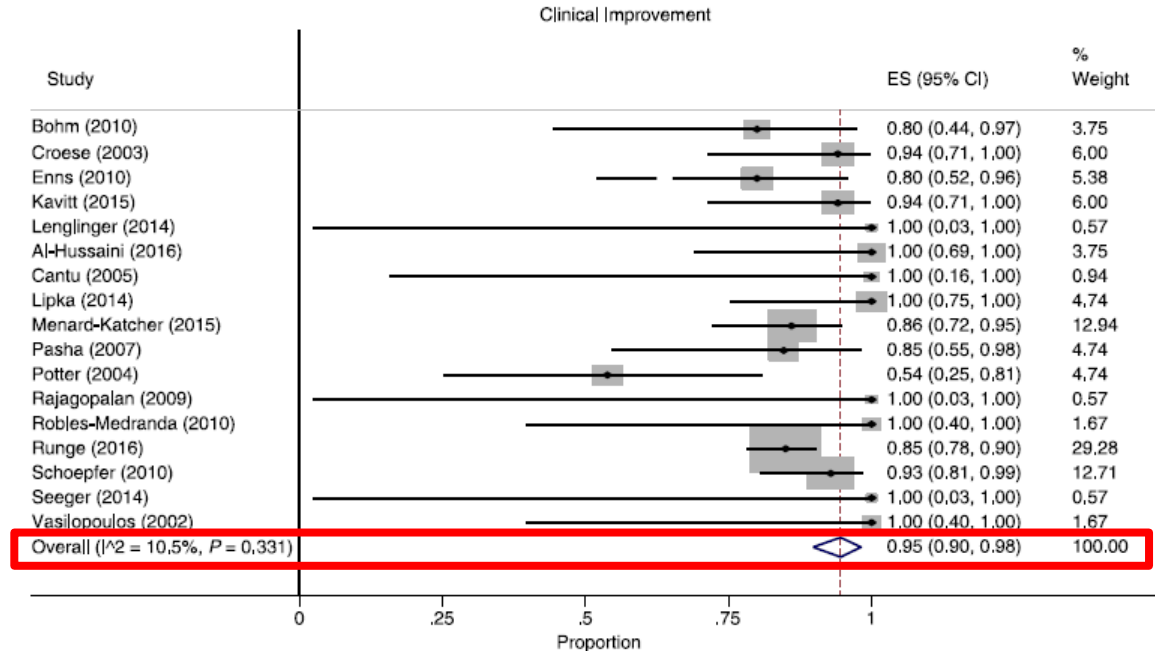
Clinical Guidance for Use of Dupilumab as Therapy: Key Considerations

- Cost
- Broad systemic immune modulation
- Less long term safety and efficacy data

Dilation in EoE



Meta-Analysis of Dilation in EoE: Clinical Improvement



Eosinophilic Esophagitis: Dilation

- Best to reserve until after effects of medical or dietary therapy assessed
- Typical effect > 1 yr
- Goal is lumen diameter of 16 mm
- *Does not address underlying disease*

Combination Therapy in EoE

- Common in clinical practice
- Limited data to guide decisions
- Issues
 - Cost
 - Adherence challenges
 - Untangling which treatment beneficial

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EoE: Response to Therapy

- Histopathology
 - < 15 eos/hpf
 - 0 eos/hpf
- Symptoms
 - Resolution of symptoms in absence of dietary modification
- *Endoscopy*
 - Reduction of inflammatory features
 - Maintenance of esophageal diameter \geq 16 mm

IMPACT: Adaptations

- **I**mbibe fluids with meals
- **M**odify food
- **P**rolong meal times
- **A**void hard textures
- **C**hew excessively
- **T**urn away tablets/pills

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Rationale for Chronic Therapy

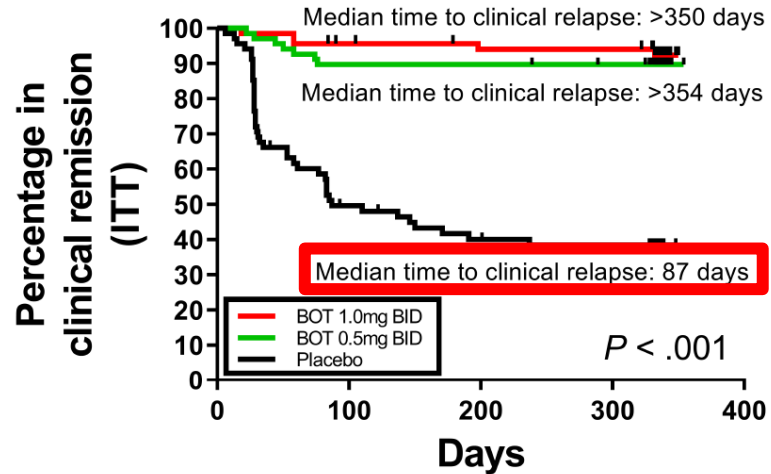
- Disease persists without treatment:
 - Natural history studies
 - Placebo arms of clinical trials
- Prolonged disease duration without treatment leads to fibrostenotic complications
- Disease activity recurs rapidly after cessation of therapy

Control of Inflammation Decreases Need for Dilation

	Nonresponders (N=28)	Responders (N=27)	P value
Esophageal diameter after initial dilation	15.8 ± 2.7	16.6 ± 2.1	0.19
Dilations needed after treatment	4.6 ± 4.6	1.6 ± 4.6	0.03

Responders: < 15 eos/hpf

Budesonide Orodispersible Tablets for 48 Weeks in EoE: Time to Clinical Relapse



Hazard ratio (HR):

BOT 1.0mg BID vs placebo: HR 0.086 ($P < .001$)

BOT 0.5mg BID vs placebo: HR 0.120 ($P < .001$)

Eosinophilic Esophagitis: Maintenance Therapy Candidates

- Narrow caliber esophagus
- Recurrent food impactions
- Strictures
- Rapid return of symptoms off therapy
- Prior spontaneous or dilation induced perforation
- Comorbid conditions increasing risk of endoscopy & dilation
- Travel to areas where food impaction causes increased risk

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New Topical Steroid Treatment Options for EoE

Company	Drug	Study Phase	Trial Status
Shire/Takeda	Premixed budesonide slurry	3	Completed
Ellodi	Fluticasone orally disintegrating tablet	3	Ongoing
Falk Pharma	Budesonide orally dispersible	Approved in Europe	Completed

Novel Biologic Treatment Options for EoE

Company	Drug	Study Phase	Mechanism
Celgene	CC-93538 (SQ)	3	IL-13 monoclonal antibody
Allakos	AK-002 (Lirentelimab) (IV)	Completed	Siglec-8 monoclonal antibody [eosinophil apoptosis + inhibits mast cell activation]
Astra Zeneca	Benralizumab (SQ)	Completed	Eosinophil IL-5 α receptor monoclonal antibody (depletes eosinophils)
Astra Zeneca	Tezepelumab (SQ)	3	Anti-TSLP
Arena/Pfizer	Etrasimod (PO)	2	Selective sphingosine-1-phosphate (S1P) receptor modulator partially & reversibly reduces lymphocyte levels at sites of inflammation
Revolu	IRL201104 (SQ)	2	Peptide that resets the immune system by preventing the chronic pro-inflammatory immune response
CSL Behring	Zemaira (IV)	2	Alpha 1 proteinase inhibitor
Celldex	Barzolvolimab (SQ)	2	Binds to receptor for tyrosine kinase KIT-mast cell inhibition

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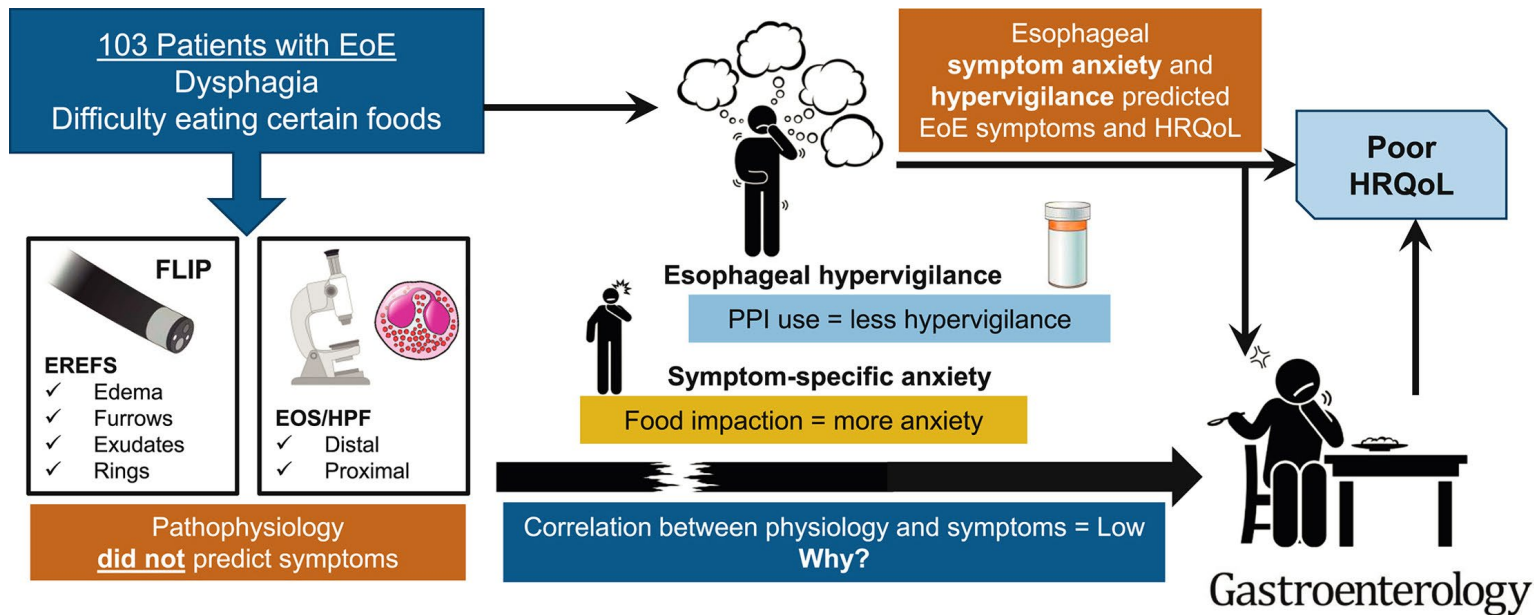
Refractory EoE

- Persistence after initial therapy:
 - Symptoms
 - Esophageal inflammation on histology or endoscopy
 - Combination of both

Patients Unresponsive to Initial Therapy: Variables to Consider

- Histologic remission with ongoing clinical symptoms vs. both histologic and clinical non-response.
 - Compliance
 - Inadequate dosing
 - Inappropriate administration of topical steroids
 - Fibrostenosis
 - Esophageal hypervigilance

Esophageal Hypervigilance & Symptom Anxiety in EoE



Summary

- The goals of EoE therapy are symptom improvement, control of inflammation and prevention of complications of remodeling
- Shared decision making informs management of EoE
- Both dietary and medical therapy effective in most but not all EoE patients
 - Do not rely on symptoms alone to assess response to therapy
- Positioning of dupilumab evolving
- Relapse is the norm after cessation of therapy
- Multiple novel compounds to treat EoE are in the pipeline
- Beware of esophageal hypervigilance & missed remodeling when symptoms refractory

