Medical management of Eosinophilic Esophagitis: What's new?

Digestive Diseases of the Caribbean

February 9, 2024

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cgibd
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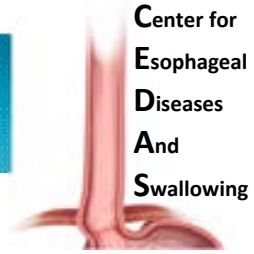

Center for
Esophageal
Diseases
And
Swallowing

Disclosures

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I will be discussing off-label uses of meds

Objectives

- Discuss the clinical and endoscopic features of eosinophilic esophagitis (EoE), as well as the diagnostic guidelines
- Discuss the medical treatment approaches to EoE
  - Will address endoscopic treatment (dilation) in the next talk!
- Understand recent research advances and management guidelines in EoE
- Provide some practical tips for EoE management

A real case…

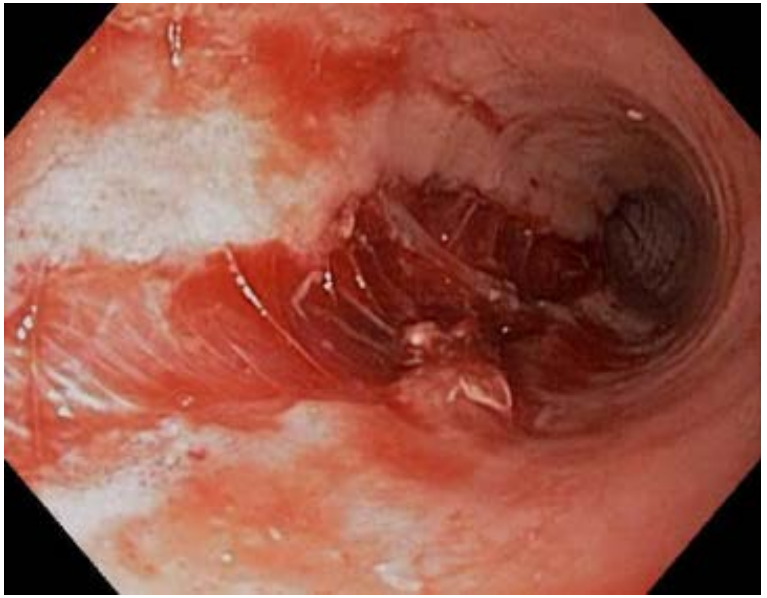
24 yo M with a 10 year history of intermittent solid food dysphagia and transient food bolus impactions

- Symptoms worsening over the past 1-2 years
- PMH: asthma, allergic rhinitis/sinusitis

Presents to the emergency department with an acute food bolus impaction that does not clear

Urgent upper endoscopy is performed

A real case…



A real case…

→ *Is this EoE?*

EoE diagnostic criteria

Clinical presentation suggestive of EoE

EGD with biopsy

Use EREFS

Esophageal eosinophilia ≥ 15 eos/hpf (~60 eos/mm^2)

Evaluate for non-EoE disorders that cause or potentially contribute to esophageal eosinophilia

PPIs now considered a treatment option

Eosinophilic esophagitis

AGREE

Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference

Evan S. Dellon, Chris A. Liacouras, Javier Molina-Infante, Glenn T. Furuta, Jonathan M. Spergel, Noam Zevit, Stuart J. Spechler, Stephen E. Attwood, Alex Straumann, Seema S. Aceves, Jeffrey A. Alexander, Dan Atkins, Nicoleta C. Arva, Carine Blanchard, Peter A. Bonis, Wendy M. Book, Kelley E. Capocelli, Mirna Chehade, Edaire Cheng, Margaret H. Collins, Carla M. Davis, Jorge A. Dias, Carlo Di Lorenzo, Ranjan Dohil, Christophe Dupont, Gary W. Falk, Cristina T. Ferreira, Adam Fox, Nirmala P. Gonsalves, Sandeep K. Gupta, David A. Katzka, Yoshikazu Kinoshita, Calies Menard-Katcher, Ellyn Kodroff, David C. Metz, Stephan Miehlke, Amanda B. Muir, Vincent A. Mukkada, Simon Murch, Samuel Nurko, Yoshikazu Ohtsuka, Rok Orel, Alexandra Papadopoulou, Kathryn A. Peterson, Hamish Philpott, Philip E. Putnam, Joel E. Richter, Rachel Rosen, Marc E. Rothenberg, Alain Schoepfer, Melissa M. Scott, Neil Shah, Javed Sheikh, Rhonda F. Souza, Mary J. Strobel, Nicholas J. Talley, Michael F. Vaezi, Yvan Vandenplas, Mario C. Vieira, Marjorie M. Walker, Joshua B. Wechsler, Barry K. Wershil, Ting Wen, Guang-Yu Yang, Ikuo Hirano, and Albert J. Bredenoord

Gastro, 2018

Clinical presentation

Symptoms:

- Dysphagia is the hallmark in adults and adolescents
  - EoE now seen in > 50% of food impactions*
  - Ask about dietary modifications and behaviors:
    IMPACT
- Heartburn
  - "Refractory reflux"
- Chest pain, abdominal pain, nausea, vomiting
- Children: failure to thrive, feeding intolerance, reflux, abdominal pain, nausea, vomiting

Imbibe fluids
Modify food
Prolong meal times
Avoid hard texture foods
Chew excessively
Turn away tablets/pills

**Desai, GIE, 2005; Kerlin, J Clin Gastro, 2007; Hirano & Furuta, Gastro 2020*

Endoscopic classification system

ORIGINAL ARTICLE

Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system

Ikuo Hirano,[1] Nelson Moy,[1] Michael G Heckman,[2] Colleen S Thomas,[2] Nirmala Gonsalves,[1] Sami R Achem[3]

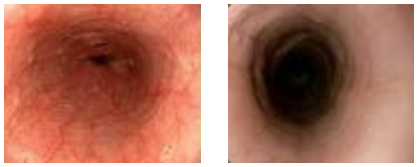
- EREFS: EoE Endoscopic Reference Score
  - Exudates (aka white plaques)
  - Rings
  - Edema (aka decreased vascularity or pallor)
  - Furrows
  - Stricture

Gut, 2013

EREFS

Grade 0 Grade 1 Grade 2 Grade 3

Edema (loss vascular markings)
Grade 0: Distinct vascularity
Grade 1: Decreased or Absent

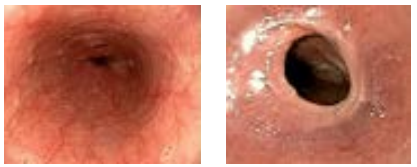


Rings (trachealization)
Grade 0: None
Grade 1: Mild (ridges)
Grade 2: Moderate (distinct rings)
Grade 3: Severe (not pass scope)

Exudate (white plaques)
Grade 0: None
Grade 1: Mild (≤10% surface area)
Grade 2: Severe (>10% surface area)

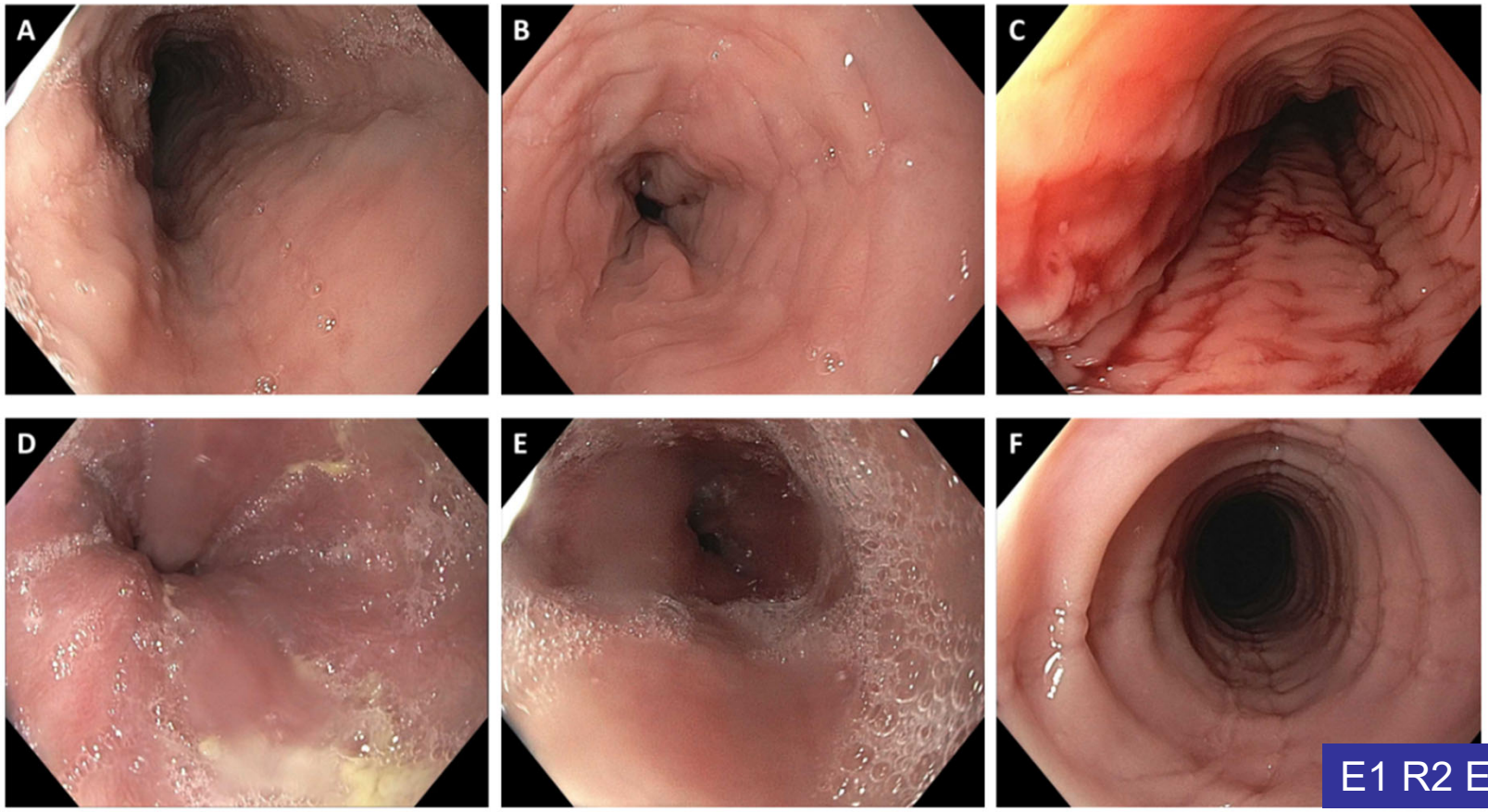
Furrows (vertical lines)
Grade 0: None
Grade 1: Mild
Grade 2: Severe (depth)

Stricture
Grade 0: Absent
Grade 1: Present



Slide courtesy of Ikuo Hirano; Gut, 2013

Optimizing the endoscopic exam



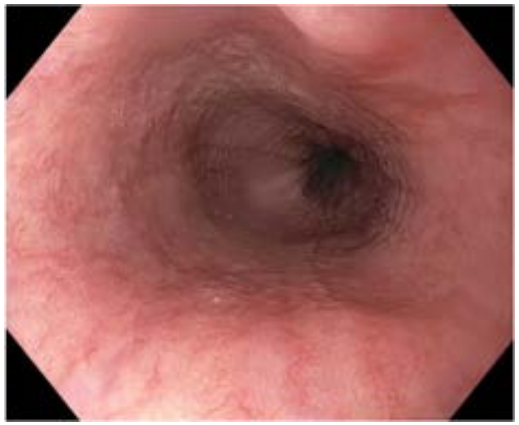
E1 R2 Ex0 F2 S13

Dellon, CGH, 2021

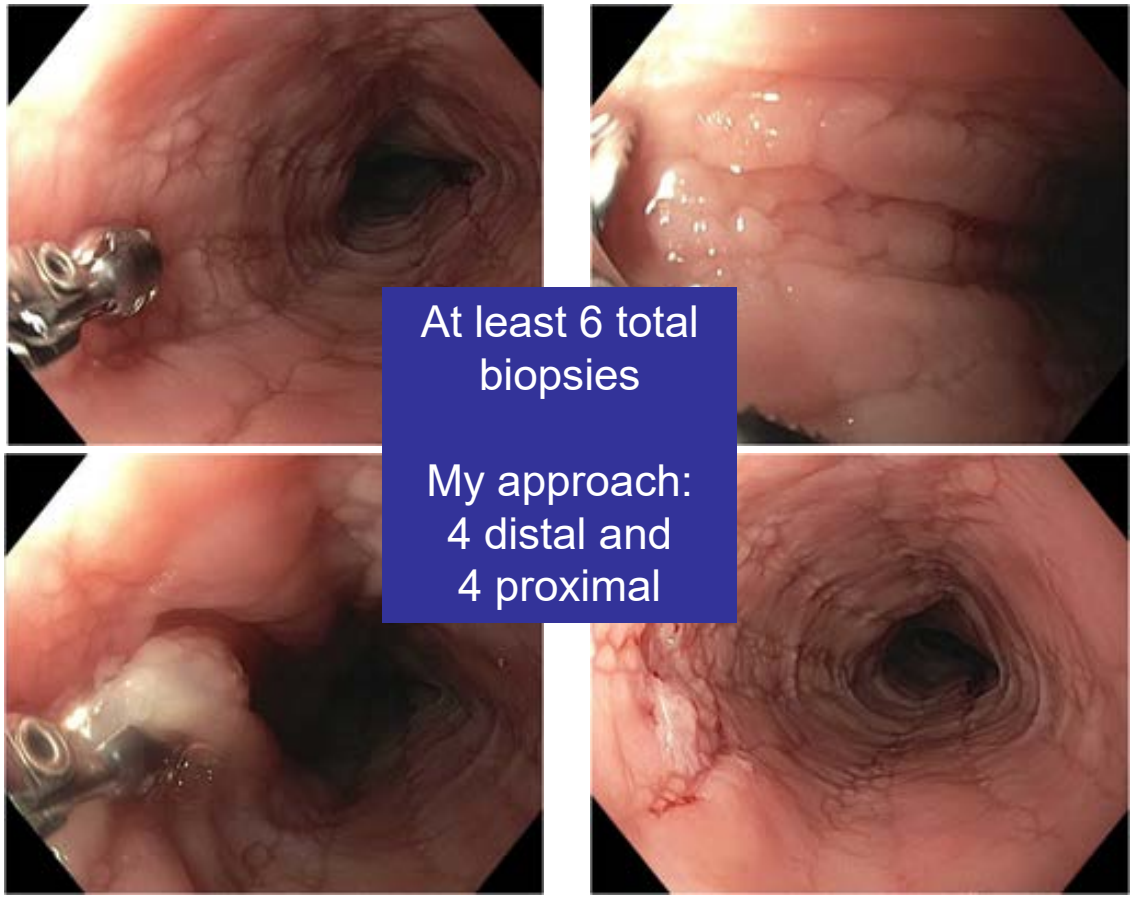
EoE and biopsy

- “Go where the money is”
- Avoid “sub-UES” area

  (Choksi et al, CGH, 2020)



- Turn and suck technique



At least 6 total biopsies

My approach:
4 distal and
4 proximal

Current EoE treatments

Non-pharmacologic

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

Pharmacologic

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

Dupilumab approved for 12+ in US (May, 2022), Europe (Jan, 2023), Canada (May, 2023)…

…and Jan 2024 for 1-11 yo!

Budesonide orodispersible tablet approved in Europe (2018), Canada, Australia, …

AGA/JTF 2020 management guidelines

Gastroenterology 2020;158:1776–1786

CLINICAL PRACTICE GUIDELINES

AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis

Ikuo Hirano,[1] Edmond S. Chan,[2] Matthew A. Rank,[3] Rajiv N. Sharaf,[4] Neil H. Stollman,[5] David R. Stukus,[6] Kenneth Wang,[7] Matthew Greenhawt,[8] and Yngve T. Falck-Ytter,[9] on behalf of the AGA Institute Clinical Guidelines Committee and the Joint Task Force on Allergy-Immunology Practice Parameters

Gastroenterology 2020;158:1789–1810

Technical Review on the Management of Eosinophilic Esophagitis: A Report From the AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters

Matthew A. Rank,[1] Rajiv N. Sharaf,[2] Glenn T. Furuta,[3] Seema S. Aceves,[4] Matthew Greenhawt,[5] Jonathan M. Spergel,[6] Yngve T. Falck-Ytter,[7] and Evan S. Dellon;[8] on behalf of the AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters collaborators

Contents lists available at ScienceDirect

ELSEVIER

Annals

Practice Parameter

AGA institute and the joint task force on allergy-immunology practice parameters clinical guidelines for the management of eosinophilic esophagitis

Check for updates

Ikuo Hirano*; Edmond S. Chan†; Matthew A. Rank‡; Rajiv N. Sharaf§; Neil H. Stollman‖; David R. Stukus¶; Kenneth Wang#; Matthew Greenhawt**; Yngve T. Falck-Ytter††; on behalf of the AGA Institute Clinical Guidelines Committee and the Joint Task Force on Allergy-Immunology Practice Parameters

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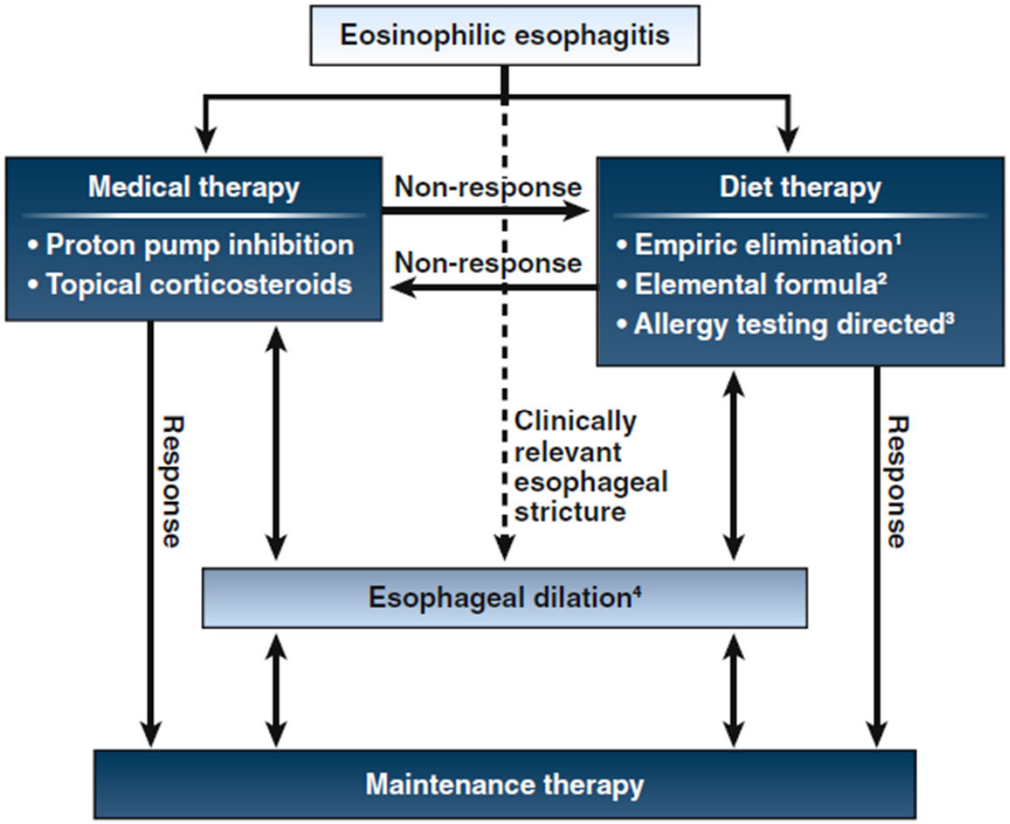
“Pre-biologic” EoE treatment algorithm



AGA, 2020

PPIs: Why in EoE?

- A recommended first-line treatment in AGA/JTF guidelines
- Histologic response rates (40-50%) in patients with EoE
- Understand the potential non-acid mediated mechanism of PPIs (and communicate these to patients)
  - Suppress Th2-mediated eotaxin-3 secretion
  - Improve esophageal barrier function
  - Improves epithelial homeostasis (re-establishes basal progenitor cells) and have multiple other effects on esophageal epithelium
- Generally start with “double dose” and if effective, wean to lower dose over time

Molina-Infante, Gut, 2016; Eluri, Curr Opin Gastroenterol, 2015; Wen, JACI, 2014; Cheng, Gut, 2013; Hara, DDW, 2021; Rochman, JACI, 2020

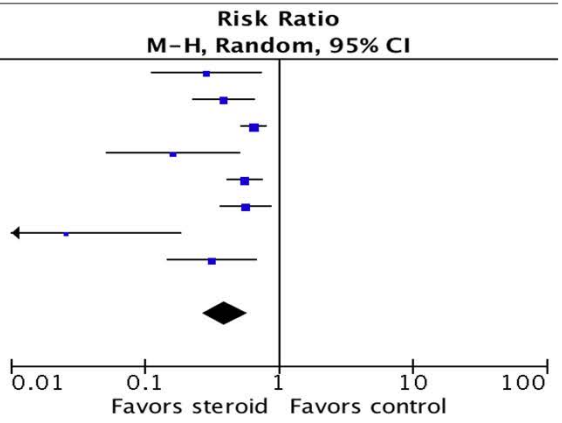
Recommendation: Topical steroids

Recommendation: In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment *(strong recommendation, moderate quality evidence)*.

Forest plot for not achieving histologic remission

Study or Subgroup	Steroids Events	Steroids Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Alexander 2012	4	21	14	21	9.4%	0.29 [0.11, 0.73]
Butz 2014	10	28	13	14	14.9%	0.38 [0.23, 0.65]
Dellon 2017	32	51	41	42	19.0%	0.64 [0.52, 0.80]
Dohil 2010	2	15	16	16	7.5%	0.16 [0.05, 0.50]
Gupta 2015	30	60	19	21	18.2%	0.55 [0.41, 0.74]
Konikoff 2006	11	21	14	15	16.2%	0.56 [0.37, 0.86]
Miehlke 2016	1	57	13	19	3.3%	0.03 [0.00, 0.18]
Straumann 2010	5	18	16	18	11.5%	0.31 [0.15, 0.67]
Total (95% CI)		**271**		**166**	**100.0%**	**0.39 [0.26, 0.58]**
Total events	95		146			

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 31.85$, $df = 7$ ($P < 0.0001$); $I^2 = 78\%$
Test for overall effect: $Z = 4.68$ ($P < 0.00001$)



Notes: Certainty in evidence rated down for inconsistency (I^2 78%) that maybe related to varying steroid dosing/delivery system, inclusion criteria, methodology to determine eosinophil density

Hirano et al, Gastro, 2020; Rank et al, Gastro 2020

Topical steroids – where do things stand?

"Esophageal-specific formulations"

- Budesonide oral suspension *(Phase 3 complete; "positive results"; not FDA-approved)*
- Budesonide orodispersible tablet *(Approved in Europe, Canada, Australia; not available in U.S.)*
- Fluticasone dissolvable tablet *(Awaiting phase 3 results; not currently available)*

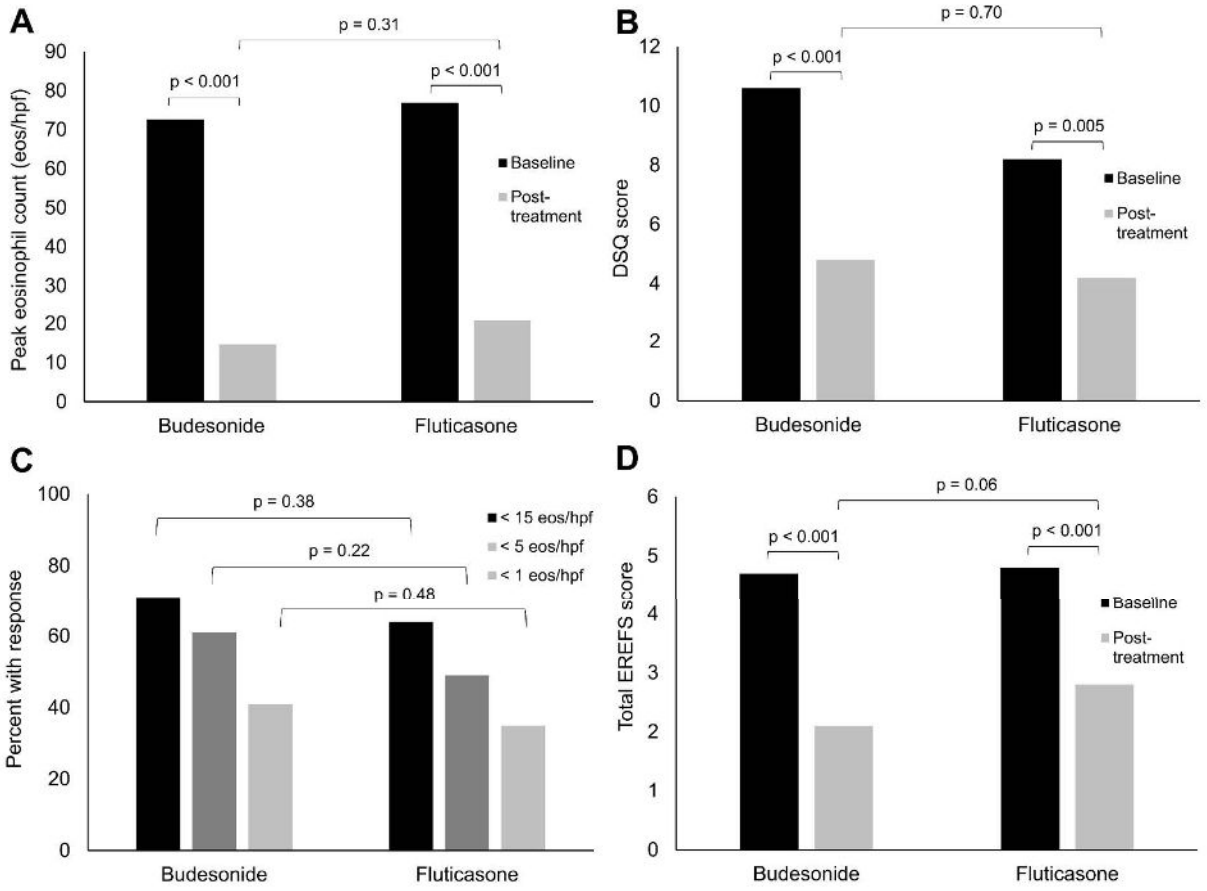
"Novel" steroid delivery

- Mometasone membrane *(Phase 2 study of ESO-101 on clinicaltrials.gov)*
- Injectable fluticasone *(Phase 1 study of EP-104IAR on clinicaltrials.gov)*

Bottom line for U.S. – still have to do "home brews" or compounded formulations of topical steroids

BOS: Hirano et al, CGH 2022; Dellon et al, CGH 2022; BOT: Lucendo et al, Gastro, 2019; FDT: Hirano et al, APT, 2020; Dellon et al, CGH 2022

Budesonide vs fluticasone



UNC SCHOOL OF MEDICINE

Dellon et al, Gastro, 2019

Topical steroid tips

Dosing in adolescents/adults:

- 2mg/d of budesonide; 1760 mcg/d of fluticasone from inhaler
- Take after breakfast or before bed; no eating or drinking for 30-60 mins
- Can consider compounded formulations*

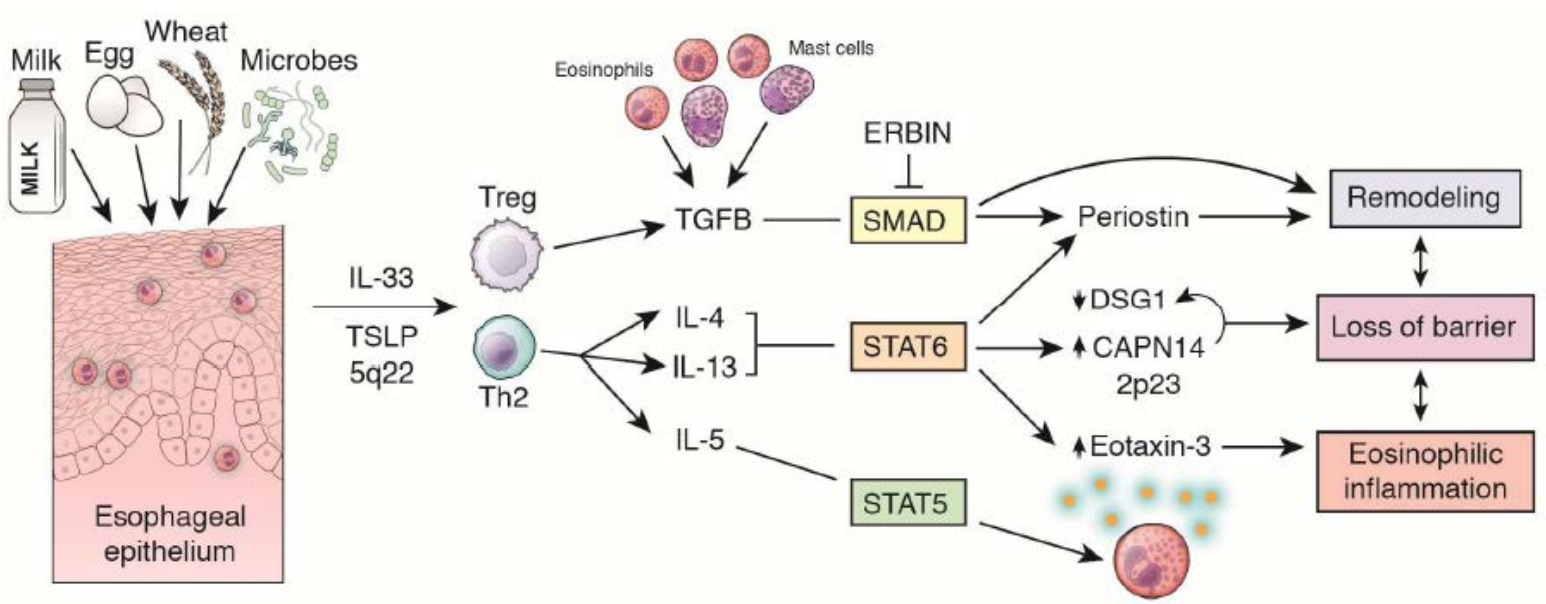
Instruction – need to spend the time to explain this

Pitfalls:

- Insurance approval; cost
- Spacer; doses; concentration; viscosity; etc…

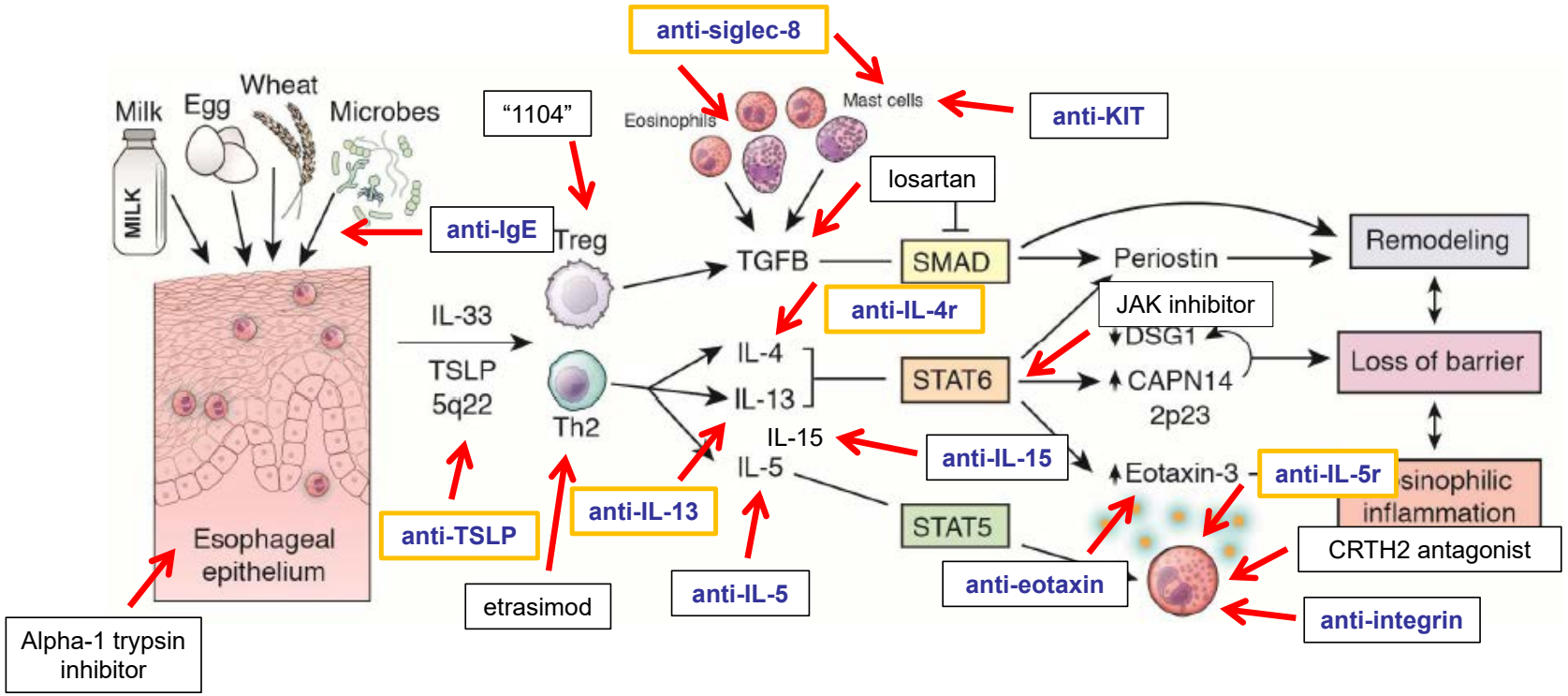
**Reed et al, J Gastroenterol Hepatol Res, 2018; Ketchem et al, Dis Esoph, 2021*

Novel treatment targets in EoE



O'Shea et al, Gastroenterology, 2018; Wechsler et al, JACI, 2018; Greuter et al, JACI, 2020

Novel treatment targets in EoE

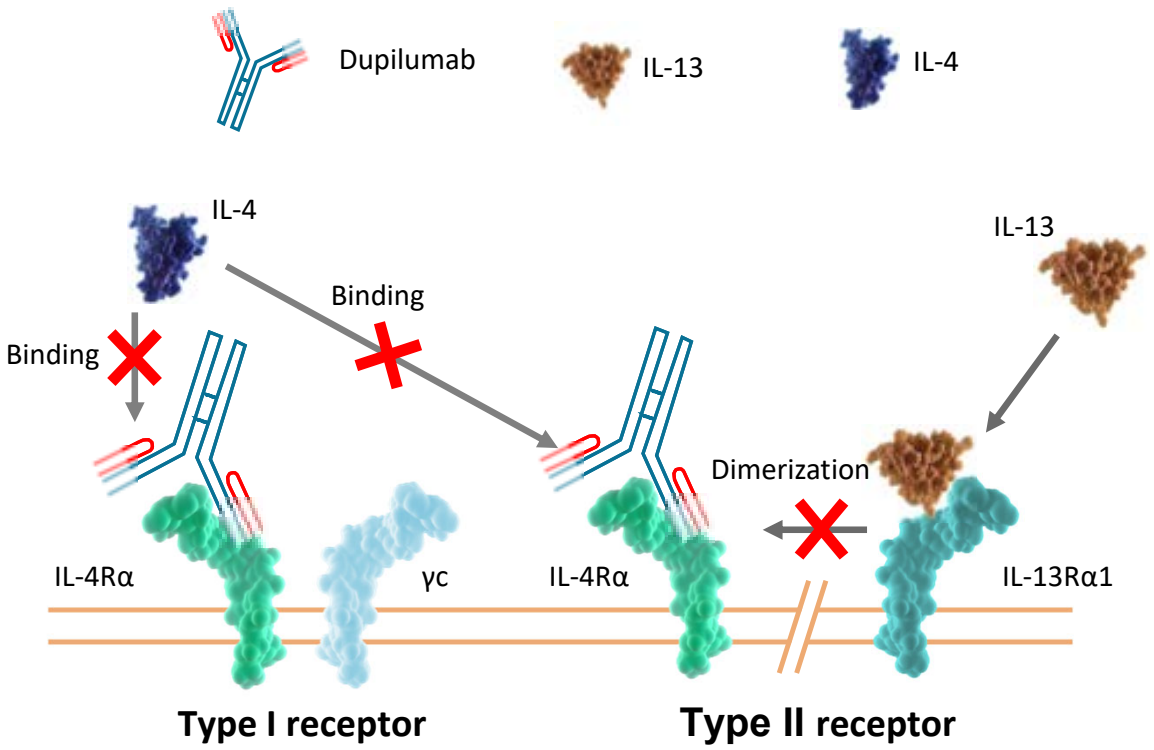


→ *Many of these may have utility for non-EoE EGIDs as well*

O'Shea et al, Gastroenterology, 2018; Wechsler et al, JACI, 2018; Greuter et al, JACI, 2020

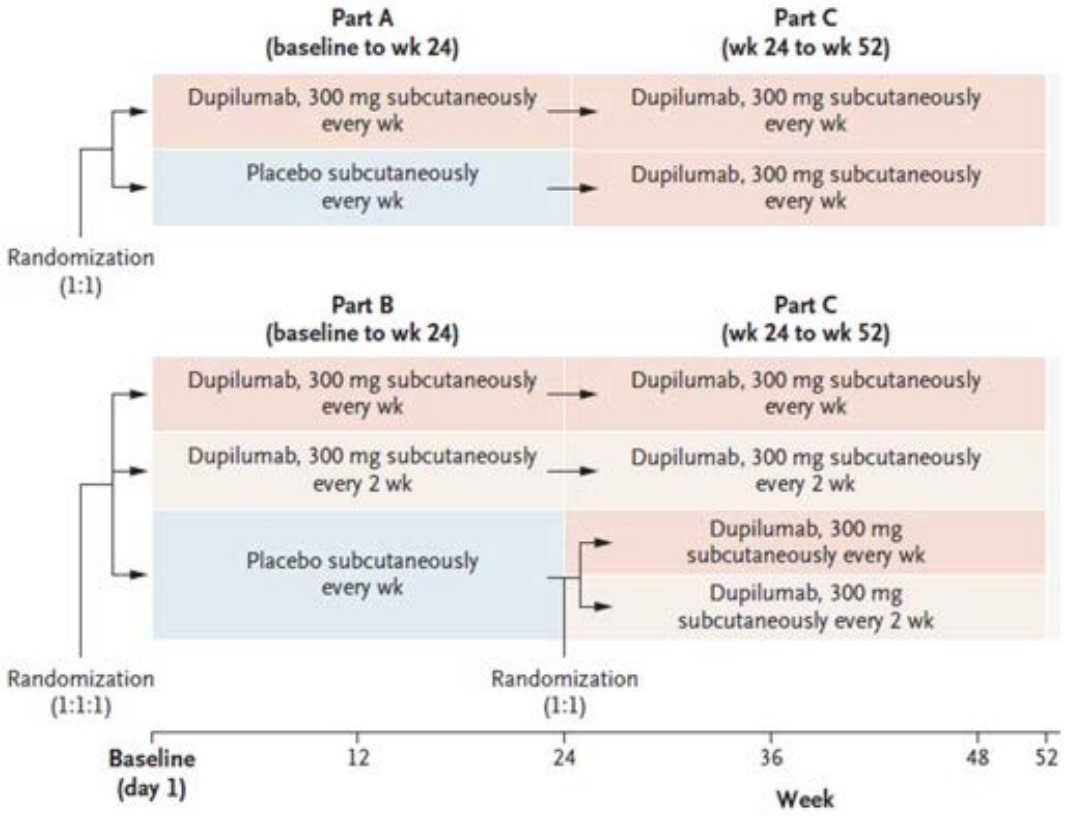
Dupilumab (anti-IL4Rα)

- Fully humanized monoclonal antibody – blocks the shared receptor for IL-4 and IL-13
- Phase 2 study showed improvements in symptoms, histology, and endoscopy findings (n=47)



Hirano, Dellon, et al, Gastro, 2019

Dupilumab – phase 3 study

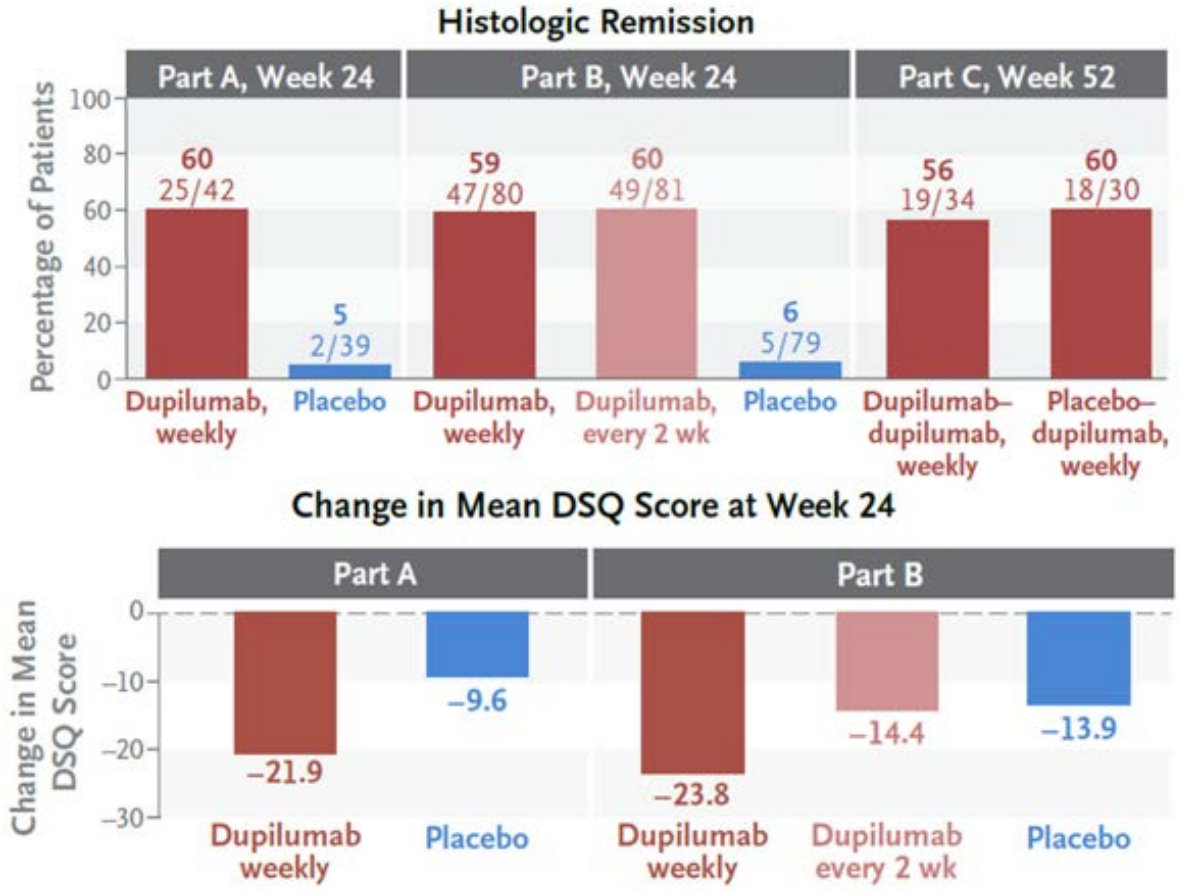


Key features of the enrolled patients:

- Mean age ~30 (age 12+ enrolled)
- All were PPI non-responsive
- ~70% with prior topical steroid use
  - ~50% refractory or intolerant
- ~40% previously dilated
- ~5 years since EoE diagnosis

Dellon, Rothenberg, et al, NEJM, 2022

Dupilumab – FDA-approved for EoE



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Dellon, Rothenberg, et al, NEJM, 2022

Dupilumab – safety

Table 2. Incidence of Adverse Events during the Treatment Period (Safety Analysis Set).*

Event	Part A		Part B			Part A–C Group in Part C	
	Dupilumab, 300 mg weekly (N=42)	Placebo (N=39)	Dupilumab, 300 mg weekly (N=80)	Dupilumab, 300 mg every 2 wk (N=81)	Placebo (N=78)	Dupilumab–dupilumab (N=40)	Placebo–dupilumab (N=37)
	number of patients (percent)						
Deaths	0	0	0	0	0	0	0
Adverse event	36 (86)	32 (82)	67 (84)	63 (78)	55 (71)	24 (60)	27 (73)
Serious adverse event†	2 (5)	0	5 (6)	1 (1)	1 (1)	0	1 (3)
Adverse event leading to discontinuation†	1 (2)	0	2 (2)	2 (2)	2 (3)	0	2 (5)
Adverse event occurring in ≥10% of patients in any group‡							
Injection-site reaction	7 (17)	4 (10)	16 (20)	18 (22)	16 (21)	4 (10)	8 (22)
Injection-site erythema	3 (7)	5 (13)	8 (10)	18 (22)	9 (12)	4 (10)	5 (14)
Injection-site pain	4 (10)	3 (8)	7 (9)	10 (12)	4 (5)	2 (5)	3 (8)
Injection-site swelling	3 (7)	1 (3)	10 (12)	7 (9)	2 (3)	2 (5)	0
Nasopharyngitis	5 (12)	4 (10)	2 (2)	4 (5)	3 (4)	1 (2)	3 (8)
Headache	2 (5)	4 (10)	6 (8)	5 (6)	9 (12)	3 (8)	2 (5)
Acne	0	1 (3)	0	2 (2)	3 (4)	0	4 (11)
Rash	0	4 (10)	2 (2)	4 (5)	0	1 (2)	0

**one SAE was felt to be related to study med – episode of SIRS*

UNC SCHOOL OF MEDICINE

Dellon, Rothenberg, et al, NEJM, 2022

Dupilumab – approach to use in EoE

- Indicated (U.S.) for EoE in patients 12 years and older, and 40 kg and up
- Dosing: 300mg SQ weekly
  - autoinjector and syringe available
- No general need for routine labs pre/post treatment or monitoring
  - immunogenicity very rare
- Prescription logistics
  - near universal need for PA
  - insurances as gatekeepers – PPI/tCS non-response often required
  - costs
- Monitoring – individualize follow-up endoscopy timing

Initial real world data for dupilumab

- 46 adults with treatment refractory EoE
- All had failed or lost response to PPI or topical steroid; 40 tried diet and all failed or lost response; half were previously enrolled in clinical trials; 85% with prior dilation (~9 dilations per person) → about 6 months on dupi

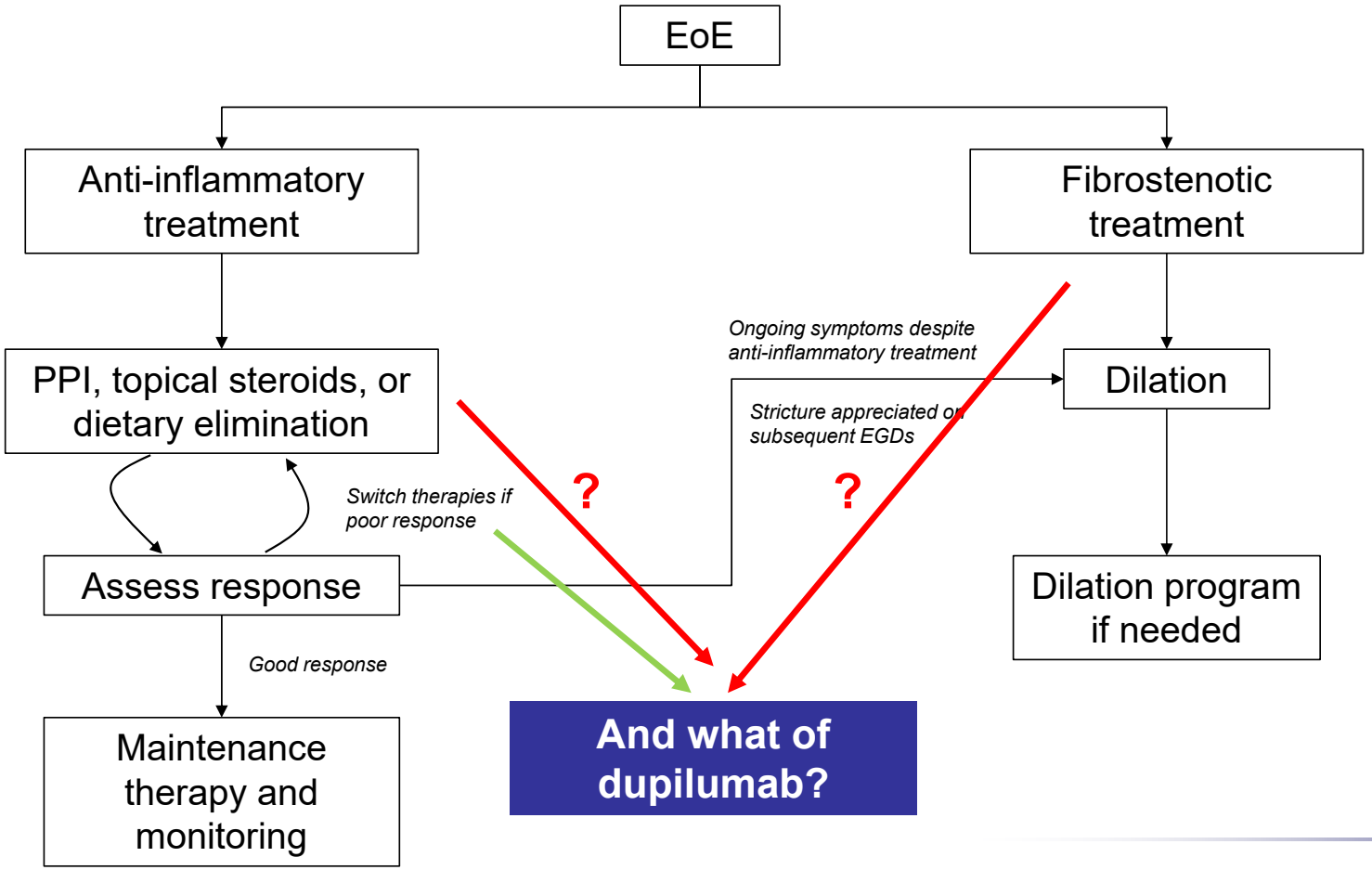
	Worst	Pre-dupilumab	Post-dupilulmab	p*	p**
Endoscopic findings (n, %)					
Total EREFS (mean ± SD)	5.01 ± 1.88	4.62 ± 1.84	1.89 ± 1.31	< 0.001	< 0.001
Stricture	34 (74)	37 (80)	33 (72)	0.13	0.71
Diameter (mean mm ± SD)	11.1 ± 4.2	13.9 ± 3.2	16.0 ± 3.0	< 0.001	< 0.001
Dilation	32 (70)	33 (72)	30 (65)	0.32	0.48
Post-diameter (mean mm ± SD)	13.6 ± 3.5	15.9 ± 2.3	17.0 ± 2.0	0.001	< 0.001
Peak eosinophil count (mean eos/hpf ± SD)	104.0 ± 67.6	70.0 ± 68.6	9.0 ± 12.0	< 0.001	< 0.001
Responses (n, %)					
< 15 eos/hpf	0 (0)	5 (11)	37 (80)	< 0.001	< 0.001
≤ 6 eos/hpf	0 (0)	4 (9)	26 (57)	< 0.001	< 0.001
0 eos/hpf	0 (0)	4 (9)	13 (28)	0.05	< 0.001
Symptom	5 (11)	8 (17)	42 (91)	< 0.001	< 0.001

Lee et al, CGH, 2023

Other emerging treatments

- Anti-IL-13 – RPC4046/cendakimab *(phase 2 EoE complete; phase 3 EoE)*
- Anti-TSLP – tezepelumab *(approved for asthma; phase 3 EoE)*
- Anti-KIT – barzolvolimab *(phase 2 EoE)*
- Anti-IL-5 - mepolizumab; reslizumab *(approved eosinophilic asthma; investigator-initiated EoE)*
- Anti-siglec-8 – AK002/lirentelimab *(EG/EGE phase 3; EoE phase 2/3)*
- Anti-IL-5r – benralizumab *(approved for eosinophilic asthma; investigator-initiated EoG; phase 2/3 EoE; phase 2/3 EoG)*
- Anti-IL-15 – proof of concept *(Vicari, mABs, 2017; prelim phase 1 data EoE/celiac)*
- Anti-α4β7 integrin *(vedolizumab; approved IBD – case reports in EoE/EGID: Kim, CGH, 2018; Nhu, AJG, 2018)*
- Sphingosine 1-phosphate (S1P) receptor modulator – etrasimod *(phase 2 EoE)*
- Immuno-regulatory protein mTB chaperonin 60.1 *(phase 2 EoE)*
- JAK1 inhibitor *(phase 1 listed on ct.gov)*
- …and more to come!

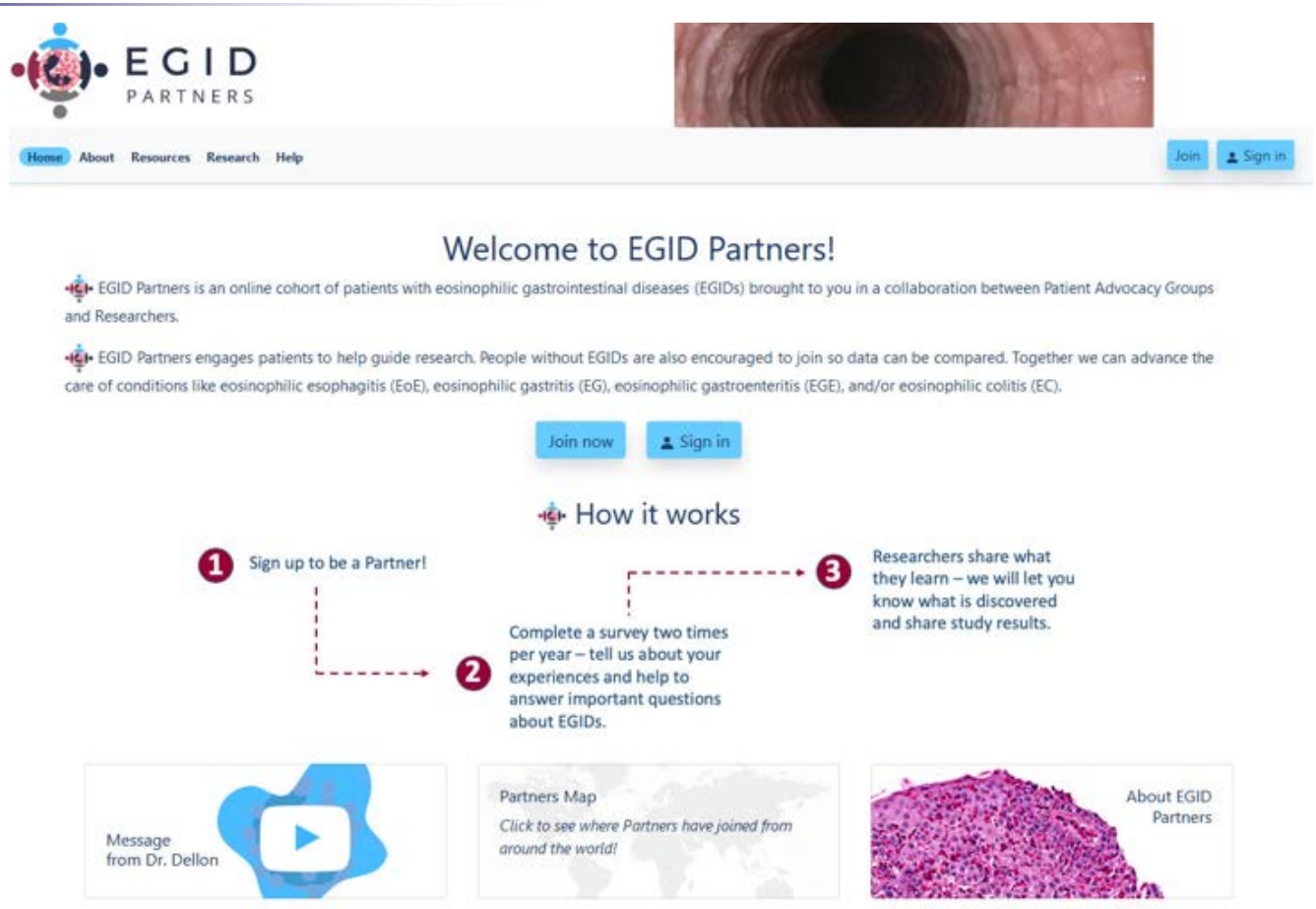
EoE management algorithm



Summary

- Updated diagnostic criteria require symptoms, esophageal eosinophilia, and exclusion of competing causes; PPI trial no longer needed
  - Do a careful endoscopic exam
- Current EoE management positions PPIs, topical steroids, and dietary elimination as first line options
  - Esophageal-specific formulations of topical steroids are being developed and optimized
  - Dupilumab now approved; ?position in treatment algorithms
- Consider anti-inflammatory treatment and fibrostenotic treatment (dilation) as two parallel and complementary approaches

egidpartners.org



Please ask your patients to check it out!

Thank you!