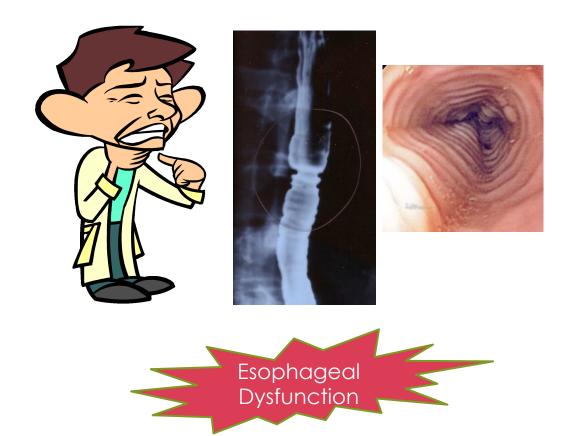


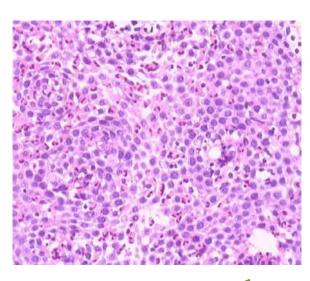


Updates in Eosinophilic Esophagitis

NIELSEN Q. FERNANDEZ-BECKER, MD, PHD

Eosinophilic Esophagitis(EoE) is a Clinicopathologic Disease







EoE Diagnostic Criteria

EoE Diagnostic Criteria

- 1. Symptoms of esophageal dysfunction
- 2. Evidence of eosinophilic inflammation 15 ≥ Eos/HPF
- 3. Exclusion of other causes of Eosinophilia

Causes of Esophageal Eosinophilia

GERD

Achalasia

Eosinophilic gastrointestinal

disease

Crohn's disease

Celiac disease

Graft vs host disease

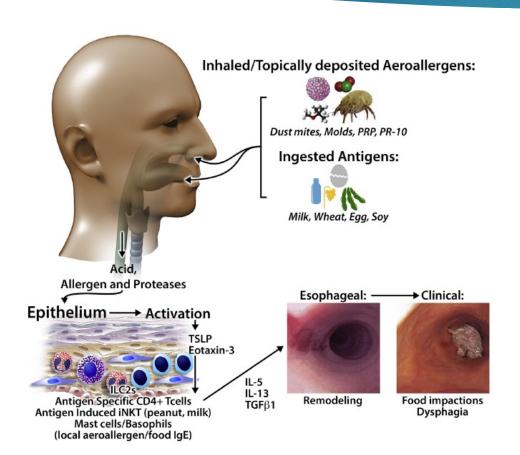
Drug reaction

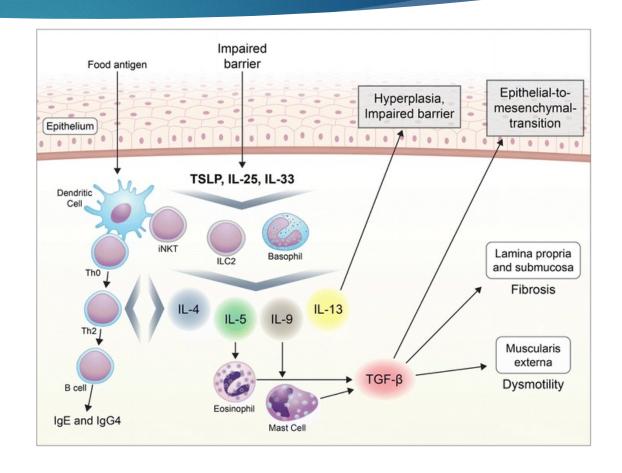
Connective tissue disorder

Vasculitis

Per New Latest AGA Guidelines Response to PPI is no longer a diagnostic criterion

EoE Pathophysiology





Eosinophilic esophagitis: Clinical Presentation

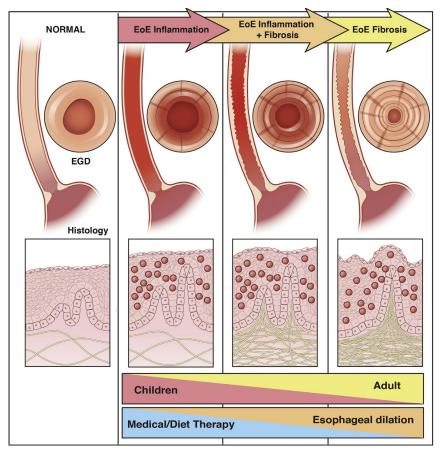
Children

- Failure to thrive
- Feeding difficulties
- Nausea
- Vomiting
- Heartburn
- Picky eating

Adults

- Dysphagia
- Eating slowly
- Solid food avoidance
- Avoidance of social eating
- Heartburn
- Chest pain





Food impaction vs Non- Food Impaction Phenotypes

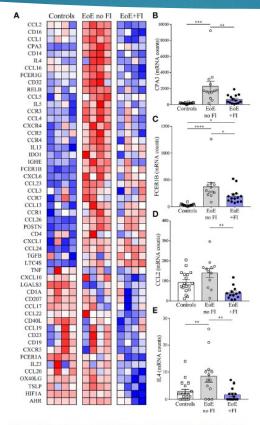
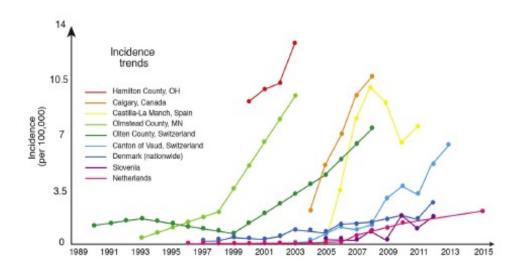


FIGURE 4 | EOE_+FI specific mRNA pattern. (A) Heat map comparison of esophageal mRNA patterns in control, Eoe no FI, and EOE_+FI patients. Relative expression of (B) CPA3, (C) FCER1B, (D) CCL2, (E) IL4 in control, EoE no FI, and EoE_+FI patients. "p < 0.05" p < 0.05" p < 0.01, ""p < 0.001", ""p < 0.001" as calculated by Dunn's multiple comparison test after Kruskal-Wallis

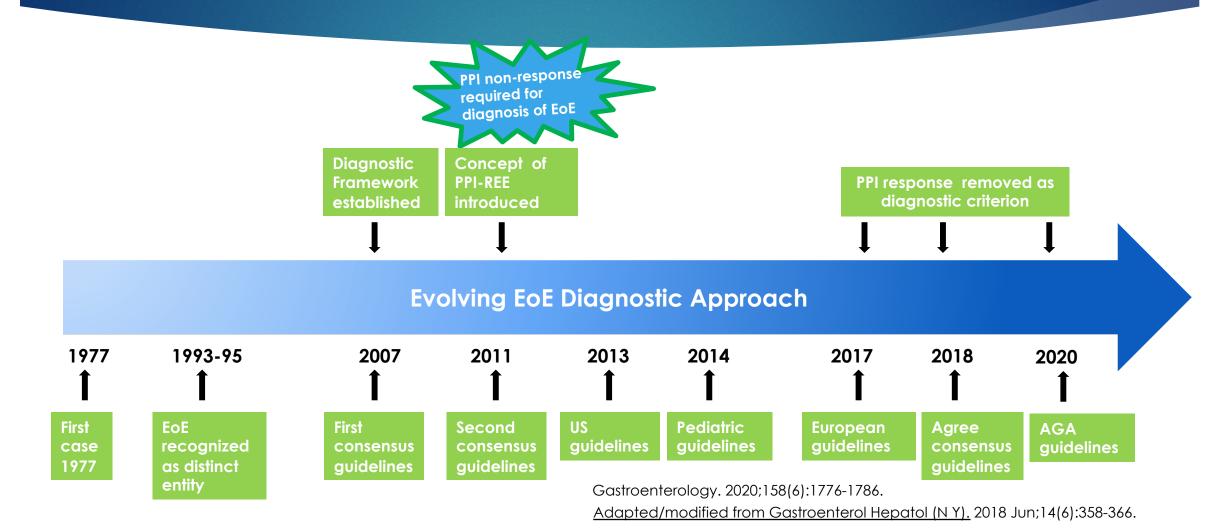
Epidemiology

- •M >F 3:1
- Most common cause of food impaction
- •Prevalence estimated at 0.5 -1/1000
- •12-23% of patients undergoing endoscopy for evaluation of dysphagia



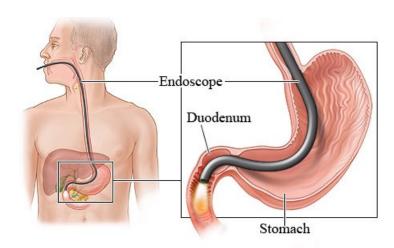
Gastroenterology 2018; 154:319-332

EoE Historical Perspective



EoE: Making the Diagnosis

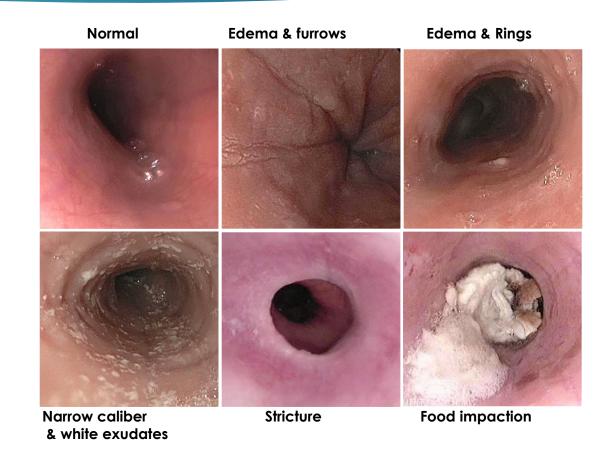
- Endoscopy (prior to PPI trial) with biopsies regardless of appearance
- 2-4 biopsies should be obtained from at least two locations in the esophagus (distal and proximal)
 - Higher the number of biopsies the higher the diagnostic yield.
- with 6-9 biopsies sensitivity close to 100%



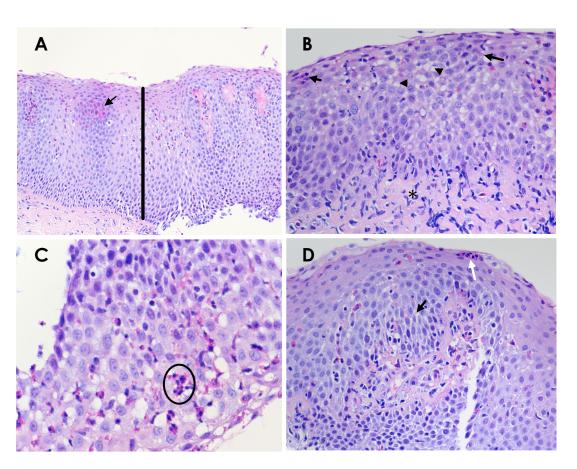
@ Healthwise, Incorporated

EoE Endoscopic Reference Score (EREFS)

EoE Endoscopi c Features	Description	Grade
Edema	Decreased vascularity/mucosal pallor	Grade 0: Distinct vascularity Grade 1: Decreased or absent vascularity
Rings	Fixed not transient like feline esophagus. Best evaluated with full insufflation	Grade 0: none Grade 1: subtle ridges Grade 2: moderate distinct rings Grade3: severe impedes passage of scope
Exudates	Can be confused with candidal esophagitis Often found along furrow borders	Grade 0: none Grade 1: Mild (<10% surface area) Grade 2: Severe (>10% surface area)
Furrows	Longitudinal/vertical "tracks" along esophagus	Grade 0: none Grade 1: Mild Grade 2: Severe (deep grooves)
Strictures	Focal or diffuse. Diameter size can be difficult to estimate	Grade 0: absent Grade 1: Present
Crepe- paper esophagus	Mucosal fragility that can manifest as sloughing from passage of endoscope	Present or absent
Narrow- caliber esophagus	Diffuse narrowing of esophagus, difficult to estimate and more accurately detected with endoFLIP or barium esophagram	Present or absent
Tug-sign	Subjective resistance met when taking biopsies	Present or absent



Microscopic Findings



Histologic Features or EoE

A: Eosinophilia (arrow) basal cell hyperplasia(bar)

B: Eosinophilia (arrow), dilated intracellular spaces

(arrowhead) and LP fibrosis (asterisk)

C: Eosinophilic abscesses (circle)

D: Eosinophilia dilated intracellular spaces (black arrow), eosinophilic surface layering and surface alteration (white arrow)

EoE Treatment: Goals of Therapy

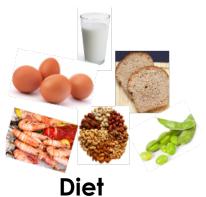


EoE Treatments



Drugs

Proton Pump Inhibitors Swallowed Topical Steroids Biologics (clinical trials)





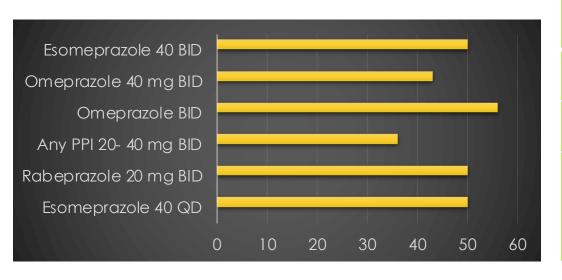
Elemental diet Allergy testing directed diet

Empiric diet (2,4,6 Elimination diet)

Savary Through Scope Balloon Dilators (TTS)

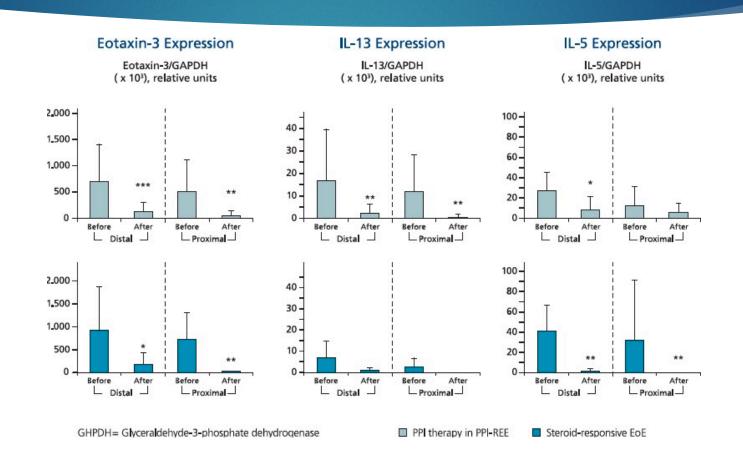
PPI as Treatment of EoE

Per New Latest AGA Guidelines conditional recommendation



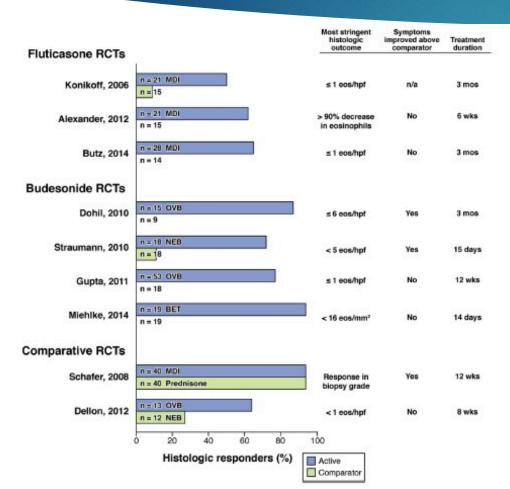
Patients	Histologic Remission (%)	l² (%)	Clinical Response (%)	l² (%)
Overall	50.5 (42.2-58.7)*	67.5	60.8 (43.4-72.2)*	80.2
Adults	49.6 (40.1-59.2)*	65.5	56.2 (41.4-70.4)*	78.3
Children	54.1 (37.7-70.0)*	69.6	64.9 (43.4-83.6)*	83.8

PPI Mechanism of Action



Swallowed Topical Steroids For Treatment of EoE

Per New Latest AGA Guidelines
Strong recommendation



Maintenance Therapy?

Pro	Cons
Highly effective inducing histologic remission	Costly
Highly effective at treating symptoms	Lack of long-term safety data
May decrease need for dilation	Risk of candida esophagitis
Reduces risk of relapse	No FDA approved formulation
	Inconvenient
	Potential for steroid resistance
	Unclear benefit in patients with mild disease phenotype
	Ideal maintenance dose is unknown

Per New Latest AGA Guidelines maintenance recommendation

Swallowed Topical Steroids: Formulations

Fluticasone INH

Fluticasone Diskus

Budesonide (Pulmicort respules) mixed with Splenda or Honey to increase viscosity and esophageal contact time.

Budesonide oral suspension (Effective in Phase III trials) Fluticasone Oral dispersable tablet (Phase III trial wrapping up) Budesonide effervescent tablet (BET) approved in Europe (Jorveza)

Promising Biologic Therapies

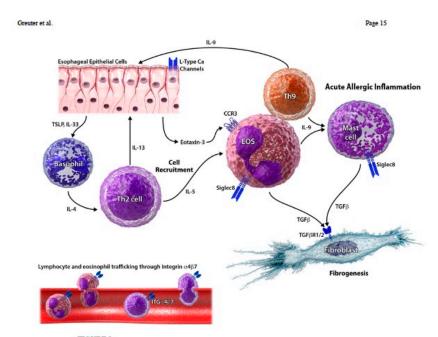


FIGURE 1:

Development pipeline of EoE-specific programs over the last two decades with progression from phase I/II to phase III stage. EG, eosinophilic gastritis.

J Allergy Clin Immunol. 2020 January; 145(1): 38–45

Annu.Rev.Med 2021. 72:14.1-14.5

Table 2 Emerging therapies for eosinophilic esophagitis

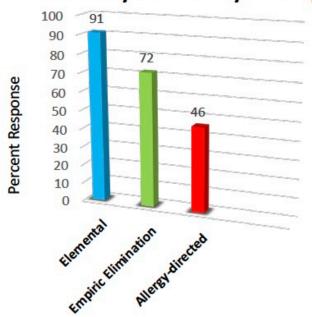
Therapeusic agent	Mechanism of action	Rouse of administration	Seudy design; patient cohore	Trial ouecome
Mepolizumsb (62-64)	Monoclonal sneibody to II5	Inerswenous	Open-label, single-arm, phase I/II; 4 adules (63)	Significane reduction in mean and peak esophageal cosinophil counts Significane improvemene in peripheral blood eosinophilis
			Randomized phase II clinical erial; 11 adules (64)	No pasienes with reduction of peak costrophils to <5 cos/hpf Significant reduction of mean costrophil counts
		0.00000000	Randomized phase II clinical erial; 59 children (62)	8.8% of pasients with peak cosinophil <5 cos/tpf Significant reduction of mean and peak cosinophil counts
Reslizumab (65)	Monoclonal sneibody to IL-5	Inerswenous	Randomized clinical erial; 226 children and adolescens	Significane reduction of peak eosinophil counts No significane improvement in symptoms
QAX576 (66)	Monoclonal sneibody to IL-13	Inerswenous	Randomized phase II clinical erial; 23 adules	Nonsignificane 40% response rate (defined as >75% decrease in peak eosinophil counts) Reduction in mean eosinophil counts
RPC4046 (67)	Monoclonal antibody to IL-13	Subcusmeous	Randomized phase II clinical erial; 99 adules	Significant reduction in mean eosinophil counts and endoscopic scrivity
Dupilumah (68)	Monoclonal antibody to IL-4α receptor	Subcusmeous	Randomized phase II clinical erial; 47 sdules	Significane improvement in symptoms Significant reduction of peak cosmophil counts and endoscopic scavity
Omalizumab (69)	Monoclonal antibody to IgE	Subcusmeous	s Randomized phase II clinical No significant reduction eosinophil courts No significant reduction symptoms	
C)C000459 (70)	Chemoseracisme recepeor- homologous molecule on Th2 cells (CRTH2) snesgonise	Oral	Remdomized phase II clinical significant reduction i counts	
AK002 (71)	Monoclonal antibody to SIGLEC-8 (depletes cosmophils)	Incravenous	Bandomized phase IA/III dinicial roll in 65 pasients with eosinophilic gractics/gastromacrisis, subgroup of 25 adults with escophageal eosinophilic infilammasion	
Infliximab (72)	Monoclonal antibody to TNF-α	Incrswenous	Open-label case series; 3 adules	Lack of resolution of eosinophilic eissue infiltration in steroid-dependent patients
Azaehioprine/6- mercapeopurine (73)	Immunomodulator, purine snalog	Oral	Uncontrolled case series; Induction of hisologic and remission in seroid-dep patients	

Abbreviations: cos/hpf, cosinophils per high-powered field; Th2, T helper type 2; TNF-a, tumor necrosis factor-a.

Dietary therapy for EoE

Per New Latest AGA Guidelines Conditional recommendation

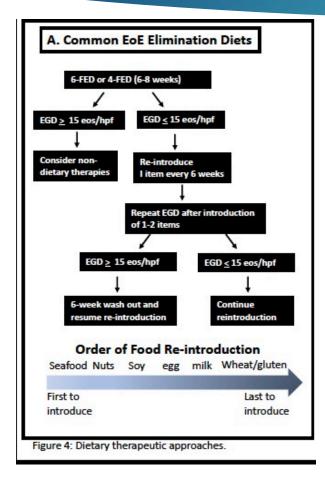
Efficacy of Dietary Therapies

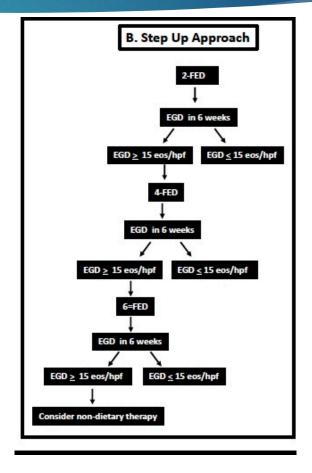


Diet Type	Description	Pros	Cons
Elemental	Amino acid formula	Most efficacious	Limited palatability Expensive Identification of specific triggers can take months May take multiple endoscopies
Empiric	Most common allergens eliminated 6-FED, 4-FED, 2- FED Step up 2,4,6 FED	Allows consumption of common table foods	Identification of specific triggers can take months May take multiple endoscopies
Allergy-directed	Elimination of selective Foods based on results of office- based allergy testing		Limited accuracy Improved methods are necessary

Annu.rev. Med. 72:14.1-14.5 Gastroenterology. 2020;158(6):1776-1786.

Dietary therapy algorithms





Dilation

Per New Latest AGA Guidelines Conditional recommendation

Characteristics and Performance of Dilation, by Type of Dilator Used

	Balloon (n = 395)	Savary (n = 91)	P
Max eosinophil count (mean eos/hpf ± SD)	55.8 ± 53.5	58.7 ± 72.2	0.73
On meds at dilation, n (%)	162 (42)	29 (34)	0.19
On diet at dilation, n (%)	60 (16)	13 (18)	0.90
Esoph diameter (mm) before dil (mean ± SD)	12.5 ± 2.9	12.7 ± 3.6	0.55
Esoph diameter (mm) after dil (mean ± SD)	15.3 ± 2.9	14.5 ± 2.7	0.02
Increase in esoph diameter (mean mm ± SD)	2.8 ± 1.2	1.8 ± 1.5	<0.001
Symptom response, n (%)*	106 (87)	24 (77)	0.34
Complications, n (%) [‡]			
Any complication	16 (4)	9 (10)	0.10
Pain	16 (4)	5 (6)	0.53
Bleeding	0	0	N/A
ER visit	1 (0.3)	4 (4)	0.005
Hospitalization	1 (0.3)	1 (1.1)	0.34
Perforation	0	0	N/A
Death	0	0	N/A

^{*}Symptom response data available for n= 153 individual dilations)

AGA Guideline Technical Review

Type of complication	Pooled Rate %
Perforation	0.4
Hospitalization	1.2
Hemorrhage	0.1

Gastroenterology. 2020;158(6):1789-1810

Gastroenterology. 2020;158(6):1776-1786.

 $^{^{\}ddagger}$ More than one complication (i.e., pain followed by er visit) occurred following a single dilation in n=6 cases.

Dilation: Treatment of Fibrostenotic disease

Goal of Therapy:

Luminal diameter of >15- 18 mm Symptomatic relief

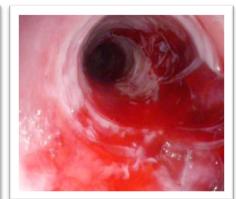
Possible complication:

Perforation Chest pain

"start low and go slow" Joel Richter

Reassess after 1-2 mm increments or after encountering resistance

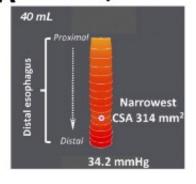


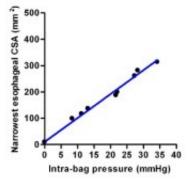


Before After

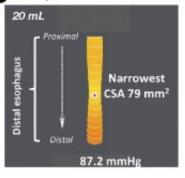
Role for EndoFLIP in Management of EoE

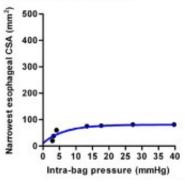
A Control subject

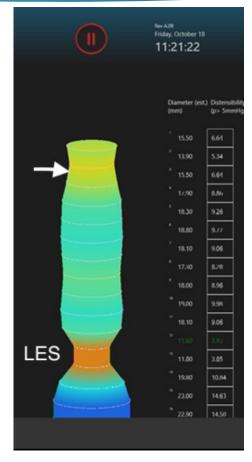




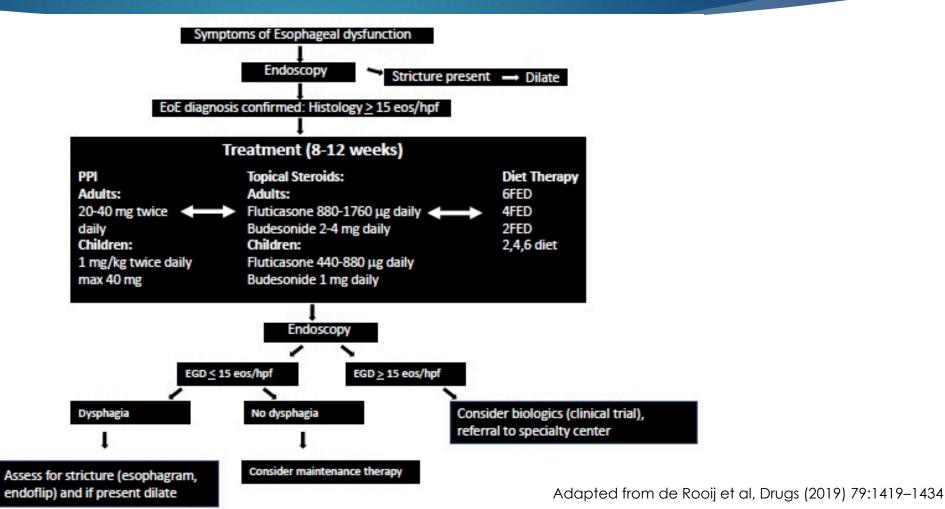
B EoE patient with narrowed distal esophagus





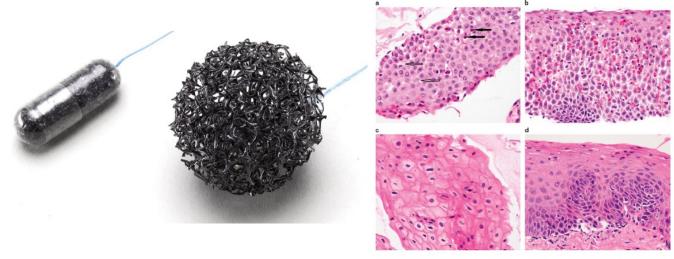


Diagnostic and Therapeutic Algorithm Summary



Future Directions: Diagnostic Modalities

Cytosponge



- Esophageal String Test
- Unsedated transnasal endoscopy
- New immunologically assays (CD4 T cell proliferation & food-specific tissue IgG4 determination)

Knowledge gaps, focus for future research

- Effectiveness of combination therapy
- Identification of patients who would benefit from maintenance therapy
- Maintenance therapy, appropriate duration and dosing
- Impact of dietary therapy on quality of life and nutritional status
- Non-invasive biomarkers to monitor

Take Home Points

- ► Eoe is a clinicopathologic disease of esophagus (symptoms of esophageal dysfunction and tissue eosinophilia (15 eos/HPF)
- Allergy driven TH2 mediated disease
- PPI non-response no longer diagnostic criterion
- PPI, Topical Steroids, Diet are effective first line therapies
- It is safe to dilate strictures in patients with Eoe with a conservative approach
- Endoflip can help guide therapy in patients with histologic response who are still symptomatic
- Novel therapies and diagnostic modalities are under investigation