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Primary Care Update: Eosinophilic Esophagitis

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Gastrointestinal Eosinophilic Diseases Program

Disclosures

- Consultant for Regeneron/ Sanofi

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Objectives

- Review the clinical presentation and multidisciplinary care of children with EoE
- Describe current and new treatments in EoE
- Identify barriers to care and collaboration that led to the development of innovative methods for disease monitoring in EoE

Gastrointestinal Eosinophilic Diseases Program (GEDP):

A Multidisciplinary Collaboration

1. Gastroenterologists (3 MDs)
2. Allergists (3 MDs)
3. Registered Dietician (3)
4. Feeding Therapist (5 SLP/ OT)
5. Allergy/ GI RNs, MAs

Outside of Clinic:

- Psychologists
- Radiologists
- Pathologists

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The 6 year old “Picky Eater”

- 6 year old male who has “never been a good eater” and is “very picky”
- Has vomiting about 1-2 times per week. He is a slow eater.
- History of atopic dermatitis, food allergies (peanut and tree nut) and asthma
- Growth is on the 5% for weight and 10% for height
- Has worked with feeding therapy

The 17 year old “Fearful Carnivore”

- 17 year old male who got “food stuck” while eating steak dinner
- History of asthma and environmental allergies
- Has had repeated episodes of food sticking for years but parents report he “takes large bites” or “eats too fast”

Eosinophilic Esophagitis: 2007- First consensus recommendations

AGA INSTITUTE

Eosinophilic Esophagitis in Children and Adults: A Systematic Review and Consensus Recommendations for Diagnosis and Treatment

Sponsored by the American Gastroenterological Association (AGA) Institute and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition

GLENN T. FURUTA,* CHRIS A. LIACOURAS,‡ MARGARET H. COLLINS,§ SANDEEP K. GUPTA,‖ CHRIS JUSTINICH,¶ PHIL E. PUTNAM,# PETER BONIS,** ERIC HASSALL,‡‡ ALEX STRAUMANN,§§ MARC E. ROTHENBERG,‖‖ and Members of the First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees##

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Furuta et al. Gastroenterology 2007.

Diagnostic Guidelines

- Eosinophilic Esophagitis (EoE) is a clinico-pathologic disease
- Clinically characterized by esophageal dysfunction
- Pathologically 1 or more biopsies show eosinophil predominant inflammation (>15 eos/high power field)

Furuta et al. Gastroenterology 2007.

Epidemiology of Eosinophilic Esophagitis (EoE)

- Prevalence is 1-4 in 10,000
- 75% of patients are male
- 75% of patients have associated atopic diseases
- **Most common cause for food impaction**
- Seen in 12-23% of patients undergoing endoscopy for difficulty swallowing

Waasdorp-Hurtado et al. JPGN 2011.
Dellon et al. Gastroenterology Clinics of North America 2014.
Furuta et al. Gastroenterology 2007.

Symptoms of EoE can vary by age

Young children

- Feeding difficulties
- Gagging
- Vomiting
- Refusal of food
- Regurgitation/ Reflux
- Food or foreign body impaction
- Dysphagia
- Abdominal pain
- Coughing with eating

Older children & adults

- Dysphagia
- Food impaction
- Chest pain
- Regurgitation/ Reflux

Furuta et al. Gastroenterology 2007.

Pediatricians & Feeding therapists:

The 6 year old “Picky Eater”

Do you have trouble swallowing? NO

The 6 year old “Picky Eater”:

Do you have trouble swallowing? NO

Compensatory behaviors

Do you…

- Drink a lot of liquids or use sauces to eat your meal? **YES**
- Cut food into small pieces or chew food a lot? **YES**
- Take longer to eat than others? **YES**
- Pocket food or keep food in your cheek? **YES**
- Avoiding foods of certain textures? (meats, breads) **YES**

Atopic Comorbidities and EoE in Children

	% among those with EoE	% among those without EoE	*P* value
Children			
Lifetime			
IgE-FA	32.44 (20.48-47.22)	7.59 (7.11-8.10)	<.001
FPIES	19.11 (9.32-35.20)	0.48 (0.39-0.59)	<.001
Asthma	26.83 (14.92-43.41)	12.17 (11.37-13.01)	.008
Atopic dermatitis/ eczema	27.53 (15.81-43.44)	5.8 (5.25-6.48)	<.001
Allergic rhinitis	43.48 (28.62-59.61)	12.74 (11.97-13.56)	<0.001
Insect sting allergy	2.83 (0.69-10.85)	2.23 (1.93-2.57)	.74
Medication allergy	3.94 (1.57-9.58)	4.15 (3.71-4.65)	.91

Cianferoni et al. Allergy 2020.

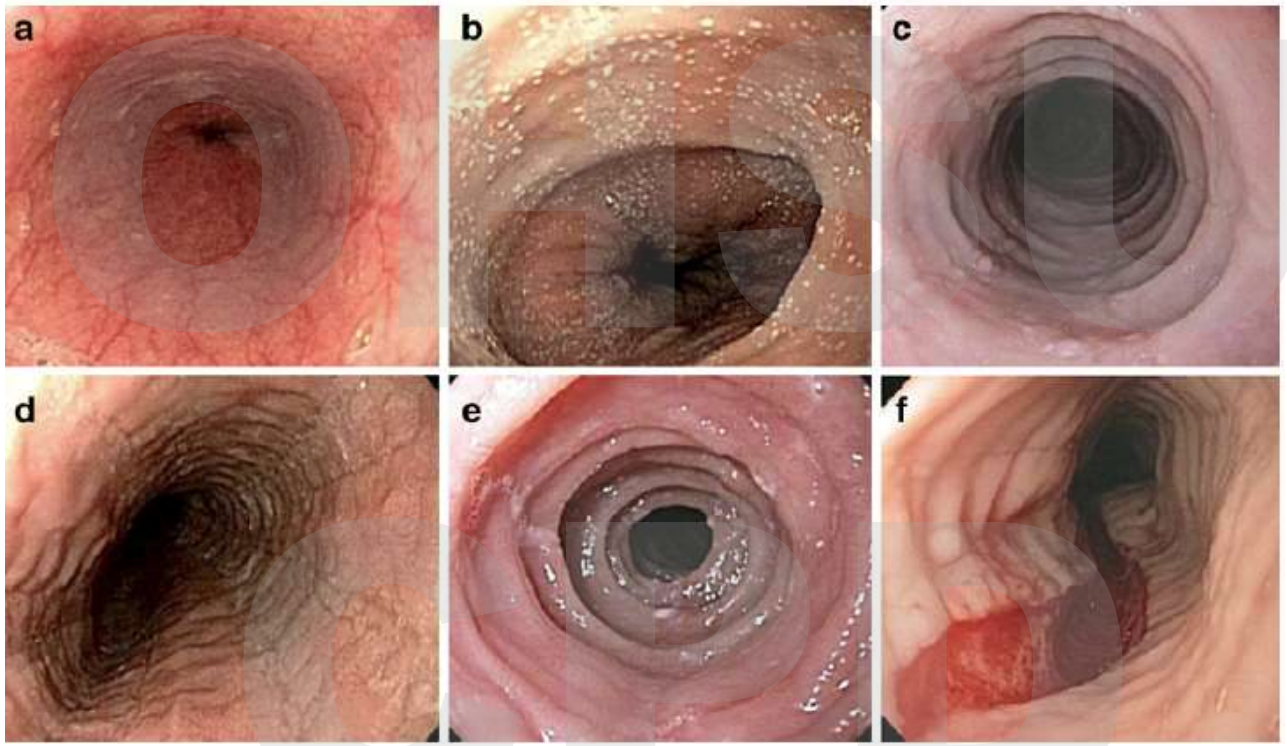
Evaluation

- May present initially to primary care, feeding therapy or other subspecialties
- Diagnosis requires endoscopy with biopsy

Normal

White Exudate

Rings



Furrows

Stricture

Longitudinal tear

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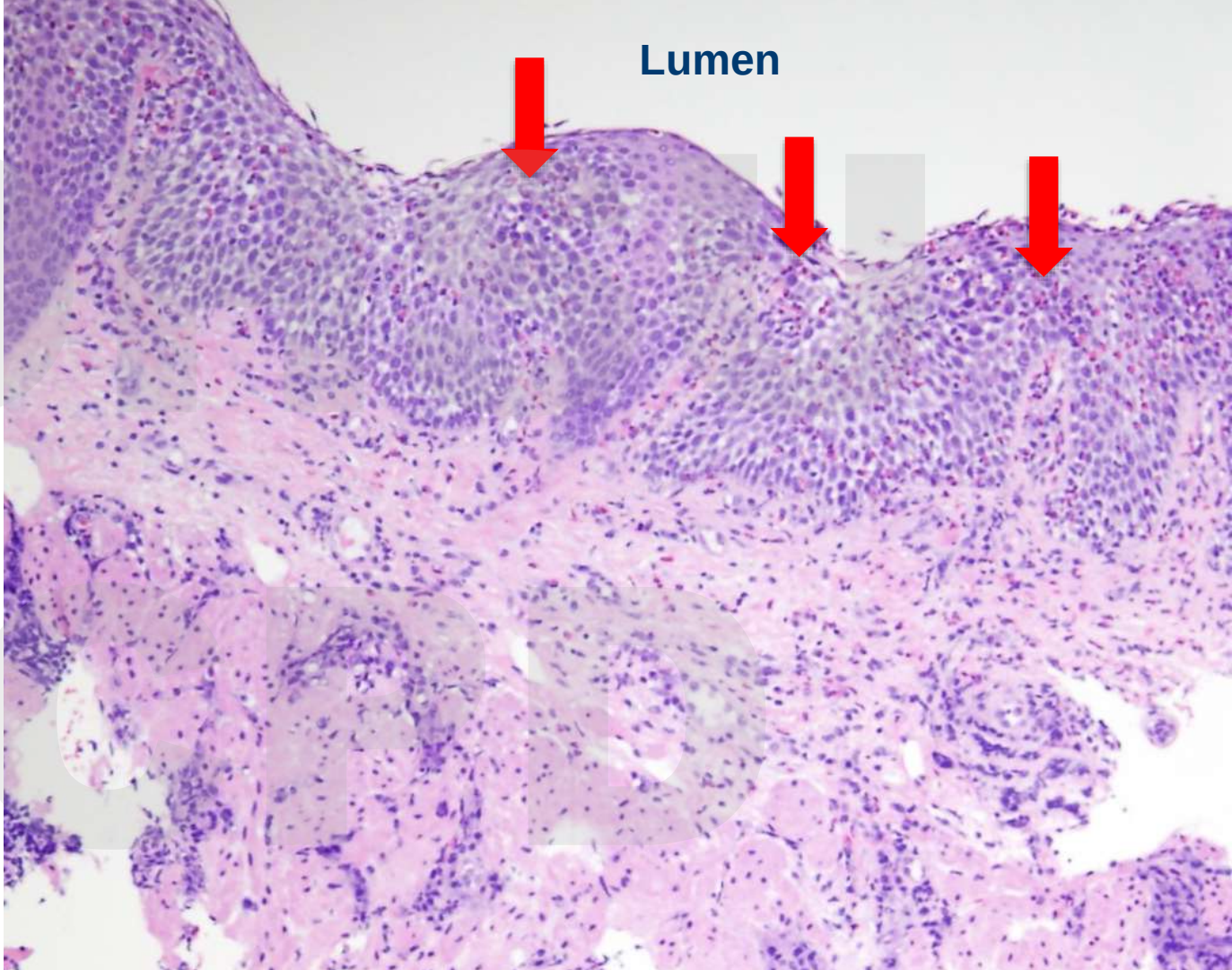
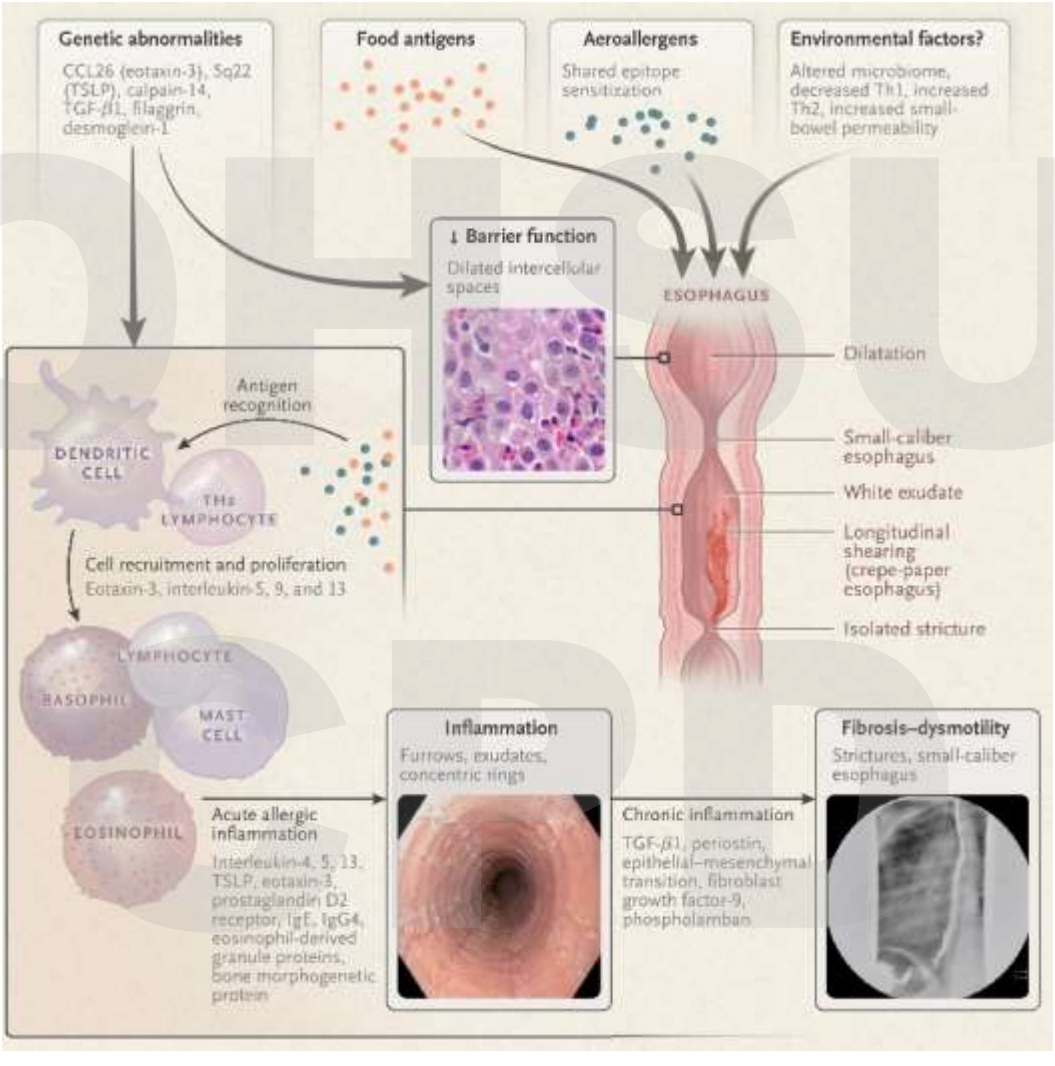
Aceves et al. Sem Immunopath 2012.

Pathologists

Esophageal Epithelium

Lamina Propria





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Furuta et al. NEJM 2015. 17

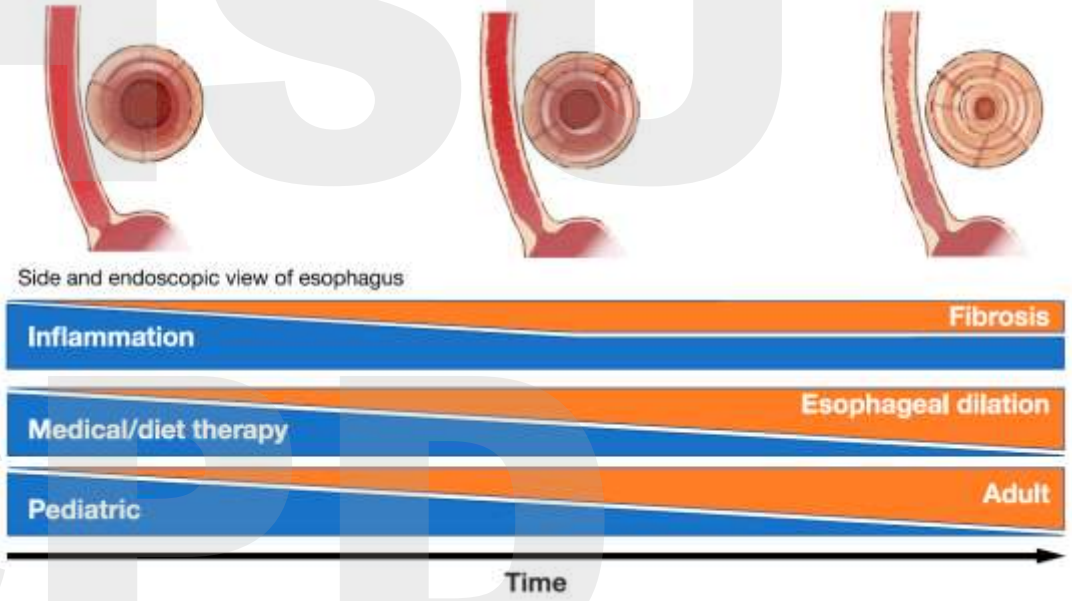
Goals of Treatment of EoE

- Improve symptoms
- Maintain growth and development
- Prevent complications
- Balance risks and benefits of treatment with Quality of Life

Furuta et al. Gastroenterology 2007.

Complications of EoE

- Esophageal stricture
- Esophageal food / foreign body impaction
- Feeding dysfunction



Furuta et al. Gastroenterology 2007.

Treatment: the 3 D's

- Drugs
  - Swallowed Topical Corticosteroids
  - PPI- Proton Pump Inhibitors
  - Biologics
- Dietary therapy
  - Elimination Diets
  - Allergy Directed Diets
  - Elemental diets
- Dilation

Treatment: Drugs

Swallowed Topical Corticosteroids

- Efficacy of topical corticosteroids ranges from 60-87%
- Typically taken twice daily
- Most commonly used:
  - Flovent or Alvesco: 2 puffs swallowed without a spacer
  - Oral Viscous Budesonide: 1-2 respules mixed for thick slurry
    - Splenda or Neocate Nutra

Konikoff et al. Gastroenterology 2006.
Aceves et al. Am J Gastroenterol 2007.
Dohil et al. Gastroenterology 2010.
Straumann et al. Gastroenterology 2010.
Alexander et al. Clin Gastroenterol Hepatol 2012.
Butz Gastroenterology 2014.

Proton Pump Inhibitors

- Previous guidelines recommend PPI trial or normal pH impedance probe to “rule out” GERD as a cause of esophageal eosinophilia
- Evidence now suggests that PPIs are better classified as treatment for EoE rather than as diagnostic criteria
- Data on PPI effectiveness varies, 50-60% response

Molina-Infante et al. Gut 2016.
Lucendo et al. Clinical Gastroenterology and Hepatology 2016.

Side Effects of Long Term PPI Use:

Side Effect	Strength of Association
Bone fractures	Weak
GI infections	**Moderate**
Pneumonia	Weak
Kidney events	Weak
Dementia	Weak
Hypomagnesemia	Weak
Rebound acid hypersecretion	**Moderate**
Iron & B12 absorption	Weak
Liver Disease	Weak

Hastrup et al. Basic & Clinical Pharmacology & Toxicology 2018.

Treatment: Biologics & Future Drugs?

FDA NEWS RELEASE

FDA Approves First Treatment for Eosinophilic Esophagitis, a Chronic Immune Disorder

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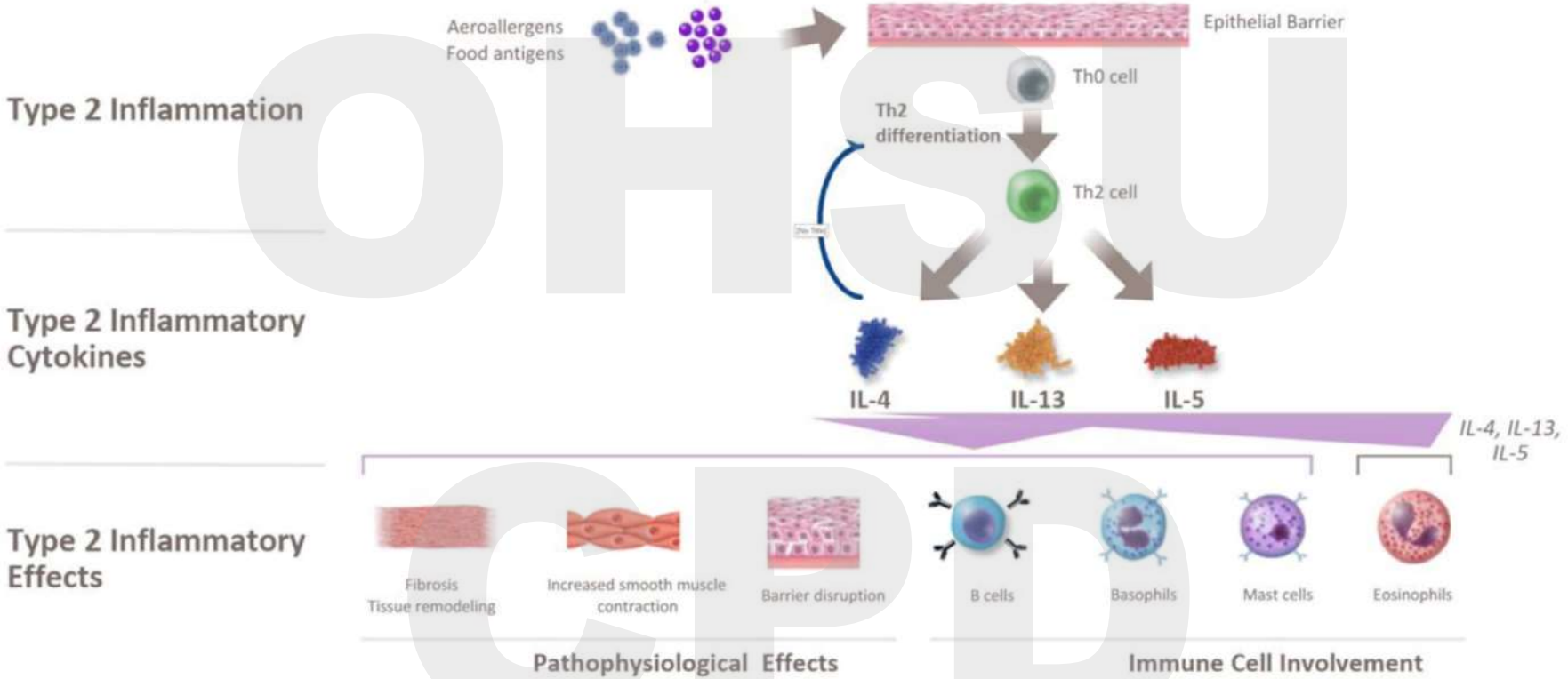
For Immediate Release: May 20, 2022

Today, the U.S. Food and Drug Administration approved Dupixent (dupilumab) to treat eosinophilic esophagitis (EoE) in adults and pediatric patients 12 years and older weighing at least 40 kilograms (which is about 88 pounds). Today's action marks the first FDA approval of a treatment for EoE.


Type 2 Inflammation
Aeroallergens
Food antigens
Epithelial Barrier
Th0 cell
Th2 differentiation
Th2 cell
Type 2 Inflammatory Cytokines
IL-4
IL-13
IL-5
IL-4, IL-13, IL-5
Type 2 Inflammatory Effects
Fibrosis
Tissue remodeling
Increased smooth muscle contraction
Barrier disruption
B cells
Basophils
Mast cells
Eosinophils
Pathophysiological Effects
Immune Cell Involvement

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

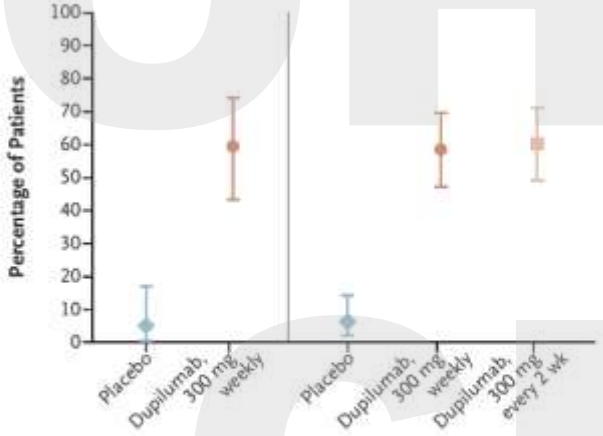
Dupilumab in Adults and Adolescents with Eosinophilic Esophagitis

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

Histologic Improvement

Dupilumab vs Placebo

A Histologic Remission at Wk 24 in Parts A and B



	Part A, Wk 24		Part B, Wk 24		
No. of Patients	39	42	79	80	81
No. of Patients with Response (%)	2 (5)	25 (60)	5 (6)	47 (59)	49 (60)

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Dellon ES, Rothenberg ME et al. NEJM. 2022

Table 2

Current Approved Use for Dupilumab

- Atopic dermatitis: Adult and pediatric patients age 6 months and older with moderate-to-severe atopic dermatitis whose diseases are not adequately controlled with topical prescription therapies or when those therapies are not advisable.
- Asthma: Add-on maintenance treatment of adult and pediatric patients age 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid-dependent asthma.
- Chronic rhinosinusitis with nasal polyposis: Add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis.
- EoE: for the treatment of adult and pediatric patients 12 years and older, weighing at least 40 kg, with EoE
- Prurigo nodularis: For the treatment of adult patients with prurigo nodularis.

Biologics Under Investigation

Table 2. Biologics Under Investigation for the Treatment of Patients With Eosinophilic Esophagitis

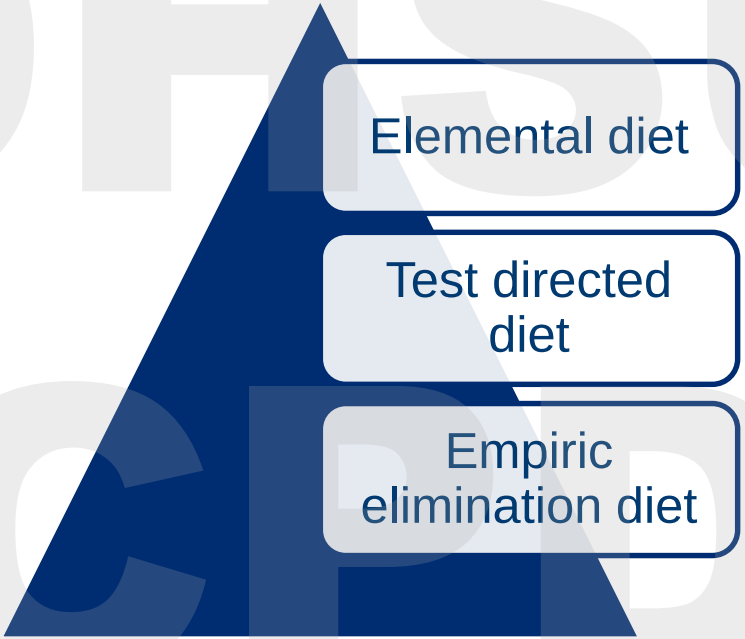
Medication	Mechanism of Action	FDA-Approved Indications	Eosinophilic Esophagitis Clinical Trial Status
Dupilumab	Monoclonal antibody to IL-4 receptor α subunit	Atopic dermatitis, asthma, rhinosinusitis with nasal polyposis	Phase 3 trials ongoing
Cendakimab	Monoclonal antibody to IL-13 receptor	None	Phase 3 trials ongoing
Lirentelimab	Monoclonal antibody to Siglec-8	None	Phase 2/3 trials ongoing
Benralizumab	Monoclonal antibody to IL-5 receptor	Asthma	Phase 3 trials ongoing
Mepolizumab	Monoclonal antibody to soluble IL-5	Asthma, hypereosinophilic syndrome, chronic rhinosinusitis with nasal polyposis, eosinophilic granulomatosis with polyangiitis	Phase 2 trials ongoing

FDA, US Food and Drug Administration; IL, interleukin; Siglec-8, sialic acid–binding immunoglobulin-like lectin 8.

Syverson et al. Gastroenterol Hepatol 2022.

Treatment:
Diet Elimination

Treatment: Dietary Approaches



Elemental Diet

- Amino Acid formulas (AAF) alone without other foods
- Overall 90.8% efficacy:
  - Children n=411 (90.4%)
  - Adults n=18 (1 study, 94.4%)
- Rarely recommended due to quality of life considerations

Kelly et al. Gastroenterology 1995.
Arias et al. Expert Rev Clin Immunol 2014.

Allergy Test Directed Diet

- Removal of specific foods based on allergy testing
- Typically a combination of prick skin tests (PST) and atopy patch tests (APT)
- Overall 46% efficacy

Mayerhofer et al. Clinical Gastroenterology and Hepatology 2023.
Arias et al. Expert Rev Clin Immunol 2014.

Empiric Elimination Diet

- Removal of specific foods most commonly associated with EoE
  - **One food elimination diet** (dairy)
    - 12 studies, overall efficacy 51%
    - Recent 1st Multicenter Randomized Trial in adults, 34%
  - **Two food elimination diet** (dairy, wheat):
    - 1 study, efficacy 43%
  - **Four food elimination diet** (dairy, wheat, soy, egg):
    - 8 studies, overall efficacy 49%
  - **Six food elimination diet** (dairy, wheat, soy, egg, fish/ shellfish, peanuts/ tree nuts):
    - 17 studies, overall efficacy 61%
    - Recent 1st Multicenter Randomized Trial in adults, 40%

Kliewer et al. The Lancet 2023.
Mayerhofer et al. Clinical Gastroenterology and Hepatology 2023.
Arias et al. Expert Rev Clin Immunol 2014.

Difficulties with Diet Elimination

- Symptoms do not always correlate with histologic improvement, therefore endoscopy is typically done after food removal and then each food group introduction

- Elemental diet, extensive elimination diets, or children with other IgE mediated food allergies may be very restricted
  - Quality of life considerations
  - Growth and Nutrition concerns

- If elemental diet or extensive elimination of foods, this requires many many endoscopies (and anesthesia) to assess if effective
  - Four food elimination diet-
    - Remove foods for 8 weeks, EGD to assess if effective
    - If effective, then add single food group for 8 weeks, then EGD to assess

Pentiuk et al. JPGN 2009.
Arias et al. Expert Rev Clin Immunol 2014.
Ho et al. J Allergy Clin Immunol Pract 2018.

Additional Foods?

1. Dairy
2. Wheat
3. Egg
4. Soy

EoE foods by biopsy (n = 602)	
Milk	211 (35%)
Egg	78 (13%)
Wheat	72 (12%)
Soy	52 (9%)
Peanut	16 (3%)
Beef	33 (5%)
Corn	39 (6%)
Chicken	32 (5%)
Potato	21 (3%)
Pork	19 (3%)
Rice	14 (2%)
Other	15 (2%)

Spergel et al. JACI 2012.

Esophageal Dilation

- Used if focal esophageal strictures or long segment esophageal narrowing
  - Focal Stricture- Balloon Dilation
  - Long segment narrowing- Bougie Dilation
- Does not treat the underlying eosinophilic inflammation
- Many patients with EoE will need serial esophageal dilations

The 6 year old "Picky Eater"

- Underwent endoscopy with biopsy
- Diagnosed with EoE
- Decided on four food elimination diet (removal of milk, wheat, soy, egg)
- Already avoiding peanut and tree nut due to food allergies
- Underwent EGD that showed EoE well controlled
- Now what?

The 17 year old "Fearful Carnivore"

- Underwent endoscopy with biopsy
- Diagnosed with EoE
- Started on PPI
- Now what?

The 6 year old "Picky Eater"

- Now what?
- Add foods one at a time and consider assessment after introduction
  - Add dairy, then EGD
  - Add egg, then EGD
  - Add wheat, then EGD
  - Add soy, then EGD
  - 4 more EGDs?

The 17 year old "Fearful Carnivore"

- Now what?
- Underwent EGD that showed active EoE on PPI
- Stopped PPI, started swallowed Flovent
- Underwent EGD that showed EoE well controlled
- Now what?
- Follow up in clinic to assess adherence and symptoms
- How often do you monitor?

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What are the barriers and unmet needs in patients with EoE?

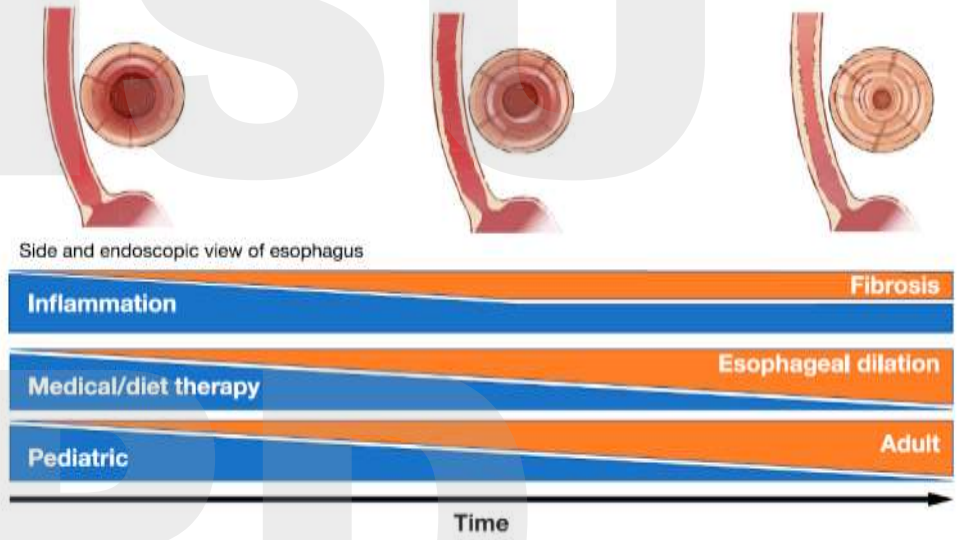
Barriers Identified

- Symptoms do not necessarily correlate with disease activity
- No biomarkers to assess disease activity
- Need for serial endoscopy to assess treatment effectiveness/ changes in therapy
- Parental concerns regarding repeated anesthesia

Pentiuk et al. JPGN 2009.
Aceves et al. GIE 2022.
Bhardwaj et al. Ann Allergy Asthma Immuol 2012.

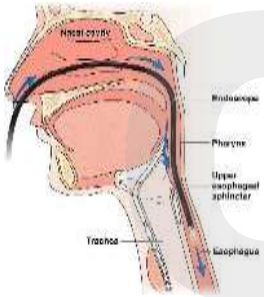
Barriers Identified

- Some patients continue to have difficulty swallowing despite histologic improvement and feeding therapy
- Is it deeper than the epithelium?



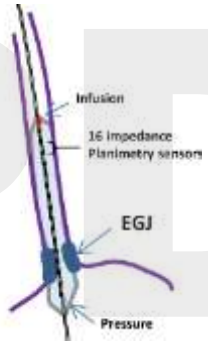
Innovations in EoE:
A Collaborative Effort

1. Transnasal Endoscopy



2. Esophageal String Test

3. EndoFlip



4. Barium Pill Esophagram

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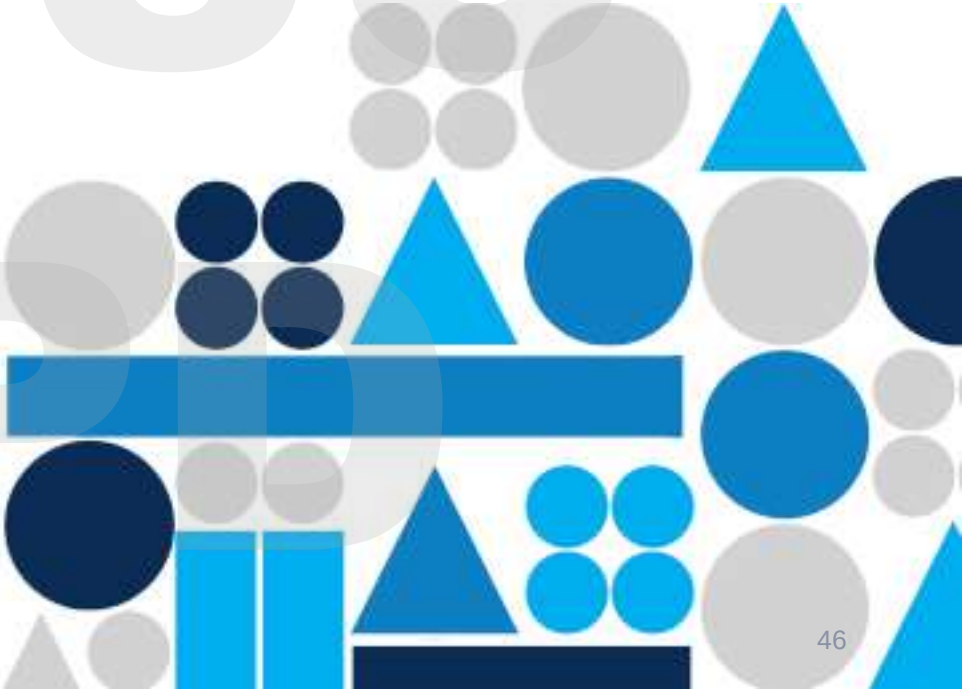
Unsedated Transnasal Endoscopy

Barrier: Need for serial endoscopy to assess treatment effectiveness



Unsedated Transnasal Endoscopy:

Development from a multidisciplinary collaboration

- Aerodigestive Program: Working together with pulmonology and ENT; routinely use bronchoscopes to intubate nasal passages in children

- Led to the development of unsedated TNE in pediatrics at Children's Hospital Colorado in 2014

Photo from Children's Hospital Colorado Foundation

Initial feasibility study

- 21 subjects (ages 8-17 years) underwent unsedated transnasal endoscopy with no serious adverse events.

- Parent willing for child undergo TNE again 100%
- Child would undergo TNE again 76%

Friedlander et al. Gastrointestinal Endoscopy 2016.

Unsedated Transnasal Endoscopy in Children with EoE

- 190 children and young adults underwent TNE from Jan 2015-Feb 2018
- Ages 3 years-22 years
- 98% success rate (294 TNEs performed, 300 attempts)
- 54 subjects (ages 6-18 years) underwent multiple TNE

Nguyen et al. Clinical Gastroenterology and Hepatology 2019.

Visual Findings in TNE

Nguyen et al. Clin Gastroenterol Hepatol 2019.

Unsedated Transnasal Endoscopy in Children with EoE

Average Charge per visit	
EGD with biopsy	$9444
Transnasal endoscopy with biopsy	$4394
Average Charge Reduction per visit	**$5051**

Nguyen et al. Clin Gastroenterol Hepatol 2019.

Adverse Events during TNE, N=178

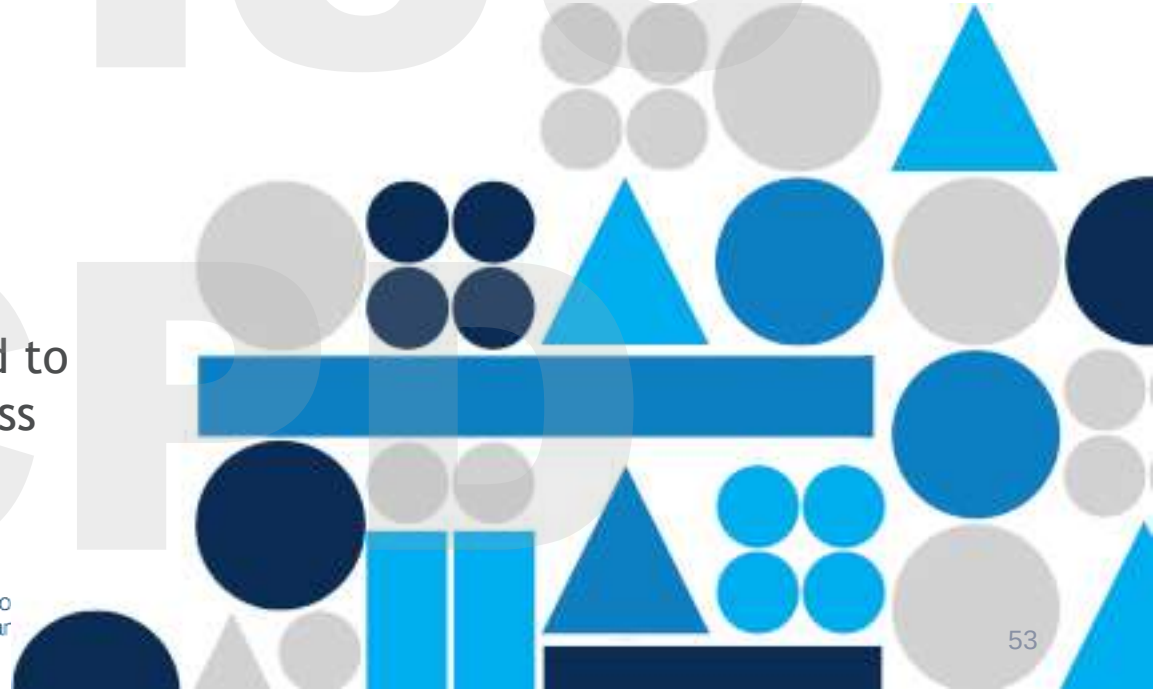
All adverse events during TNE were grade 1; No adverse events classified as grade 2 or higher

Adverse Event	Number of Subjects (%)
Vomiting	8 (4.5%)
Spit up	6 (3.4%)
Nasal Irritation	4 (2.2%)
Epistaxis	2 (1.1%)
Pre-syncope	1 (0.6%)
Anxiety	1 (0.6%)
Procedure Suspended	1 (0.6%)
No Events	155 (87%)

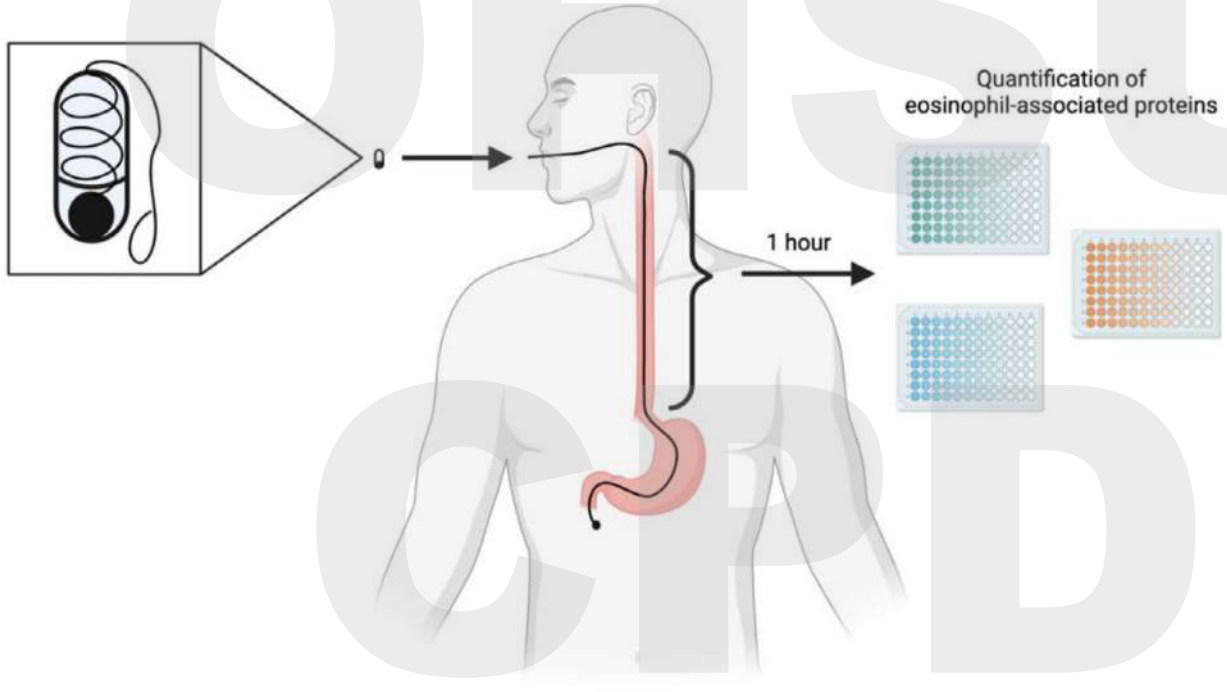
Nguyen et al. Clin Gastroenterol Hepatol 2019.

Esophageal String Test (EST)

Barrier: No biomarkers, need to assess treatment effectiveness



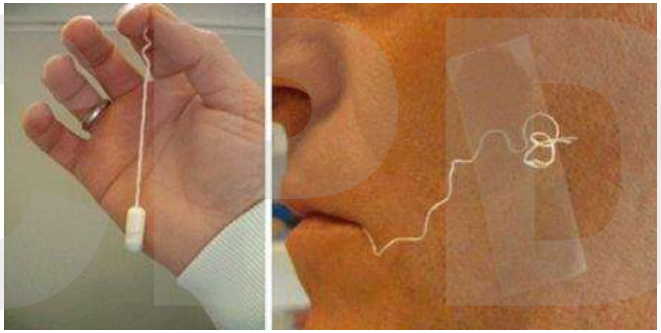
Esophageal String Test



McGowan et al. Ann Allergy Asthma Immunol 2022.

Esophageal String Test

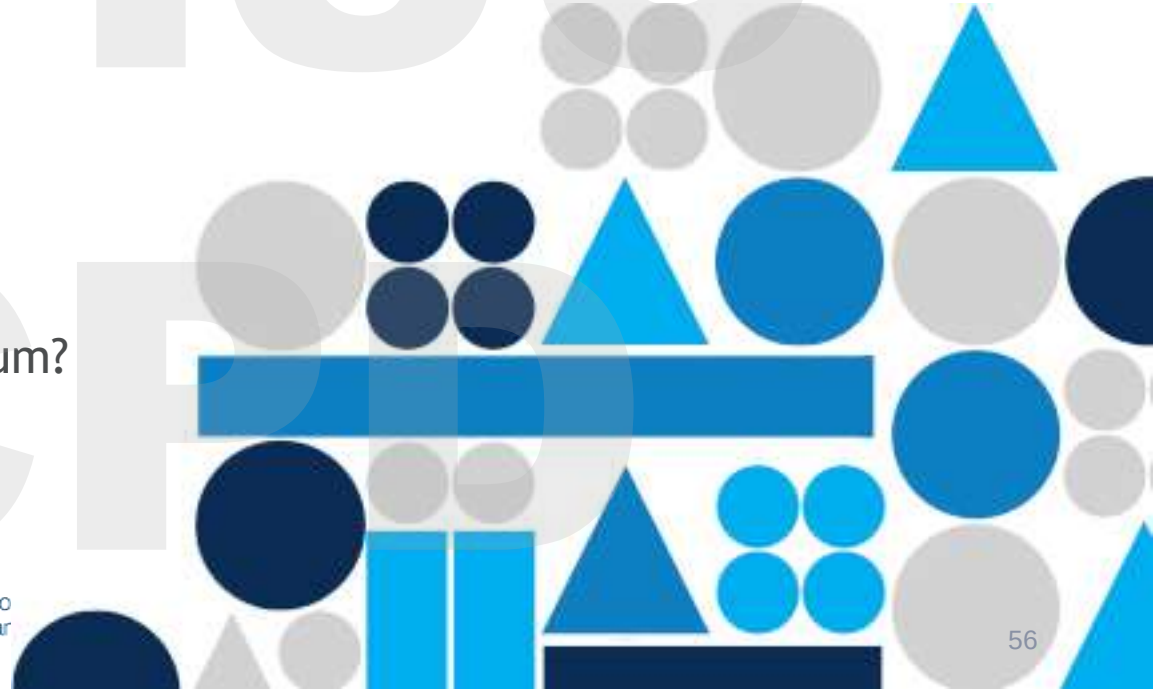
- Esophageal dwell time of 1 hour
- EST captures eosinophil-associated biomarkers (MBP and eotaxin-3) which correlate with peak eosinophil count and endoscopic visual scoring
- The 1-hour EST distinguishes active from inactive EoE in children and adults and can facilitate monitoring of disease activity in a safe and minimally invasive fashion



Furuta et al. Gut, 2013.
Ackerman et al. Am J Gastroenterol, 2019.

EndoFLIP

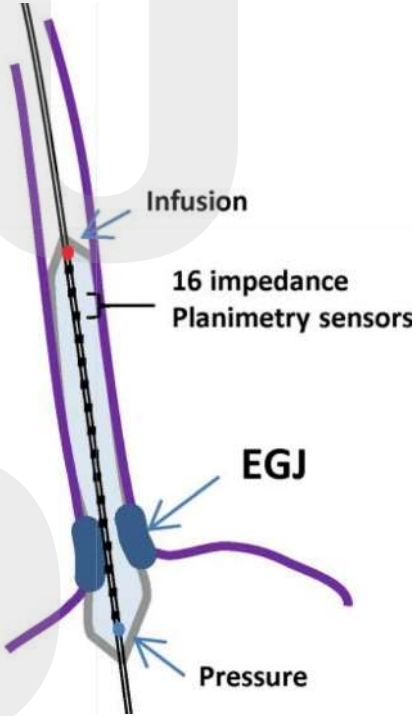
Barrier: Beyond the epithelium?



Functional Luminal Imaging Probe (EndoFLIP)

- Catheter inserted into the esophagus during endoscopy

- Measures distensibility of the esophagus



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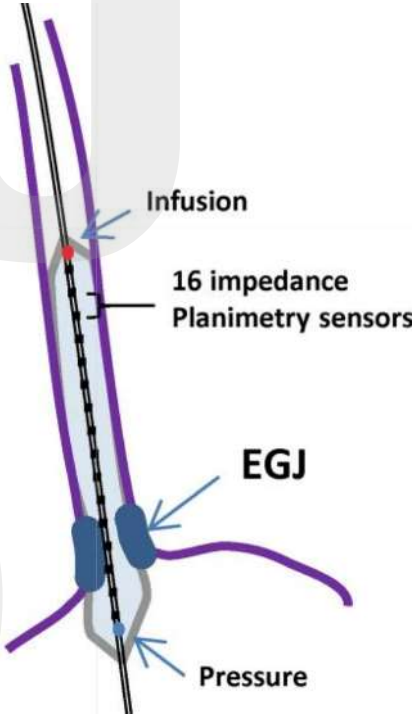
Kwiatek et al. Gastroenterology 2011.
Menard-Katcher et al. Am J Gastroenterol 2017.

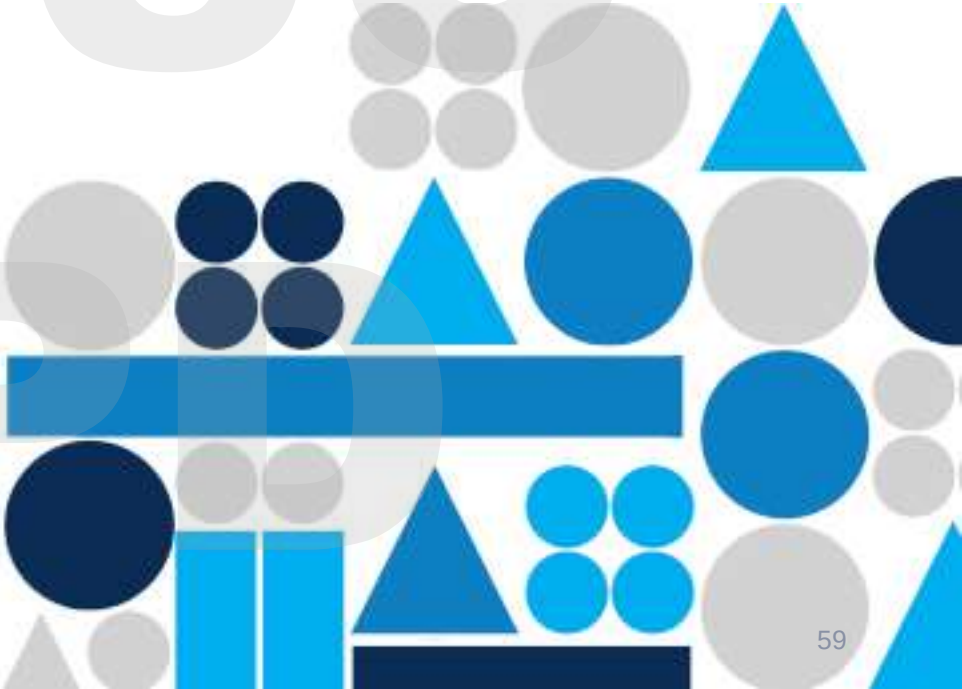
Functional Luminal Imaging Probe (EndoFLIP) in Pediatrics

- Esophageal distensibility is decreased in pediatric EoE patients
- Patients with increased disease activity have decrease distensibility
- Esophageal distensibility increases with age in the normal pediatric population



Menard-Katcher et al. Am J Gastroenterol 2017.

Barium Pill Esophagram

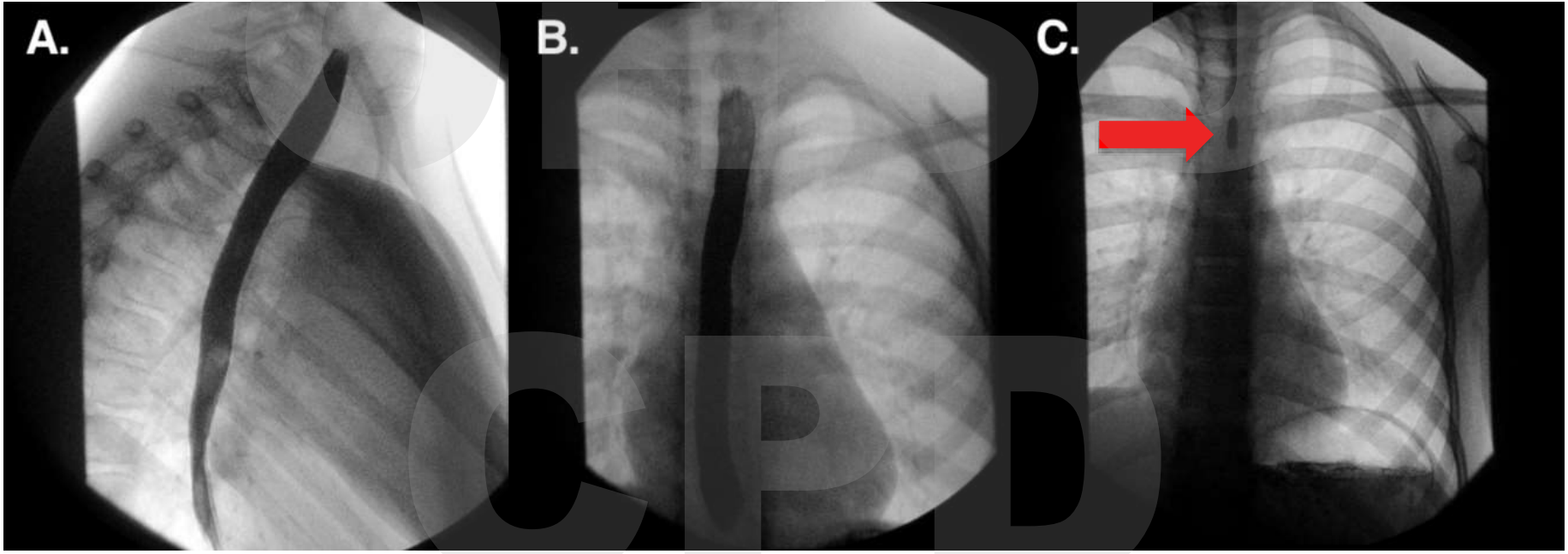


Clinical Barrier/ Observation

- Clinical conundrum: Patients with EoE continued to have dysphagia despite treatment for EoE and normal esophagram
- It is difficult to detect subtle narrowing in patients with EoE
- Identified patients with normal liquid barium esophagram who had retention of barium pill for > 5 minutes

Nguyen et al. JPGN 2020.

Barium Pill Esophagram



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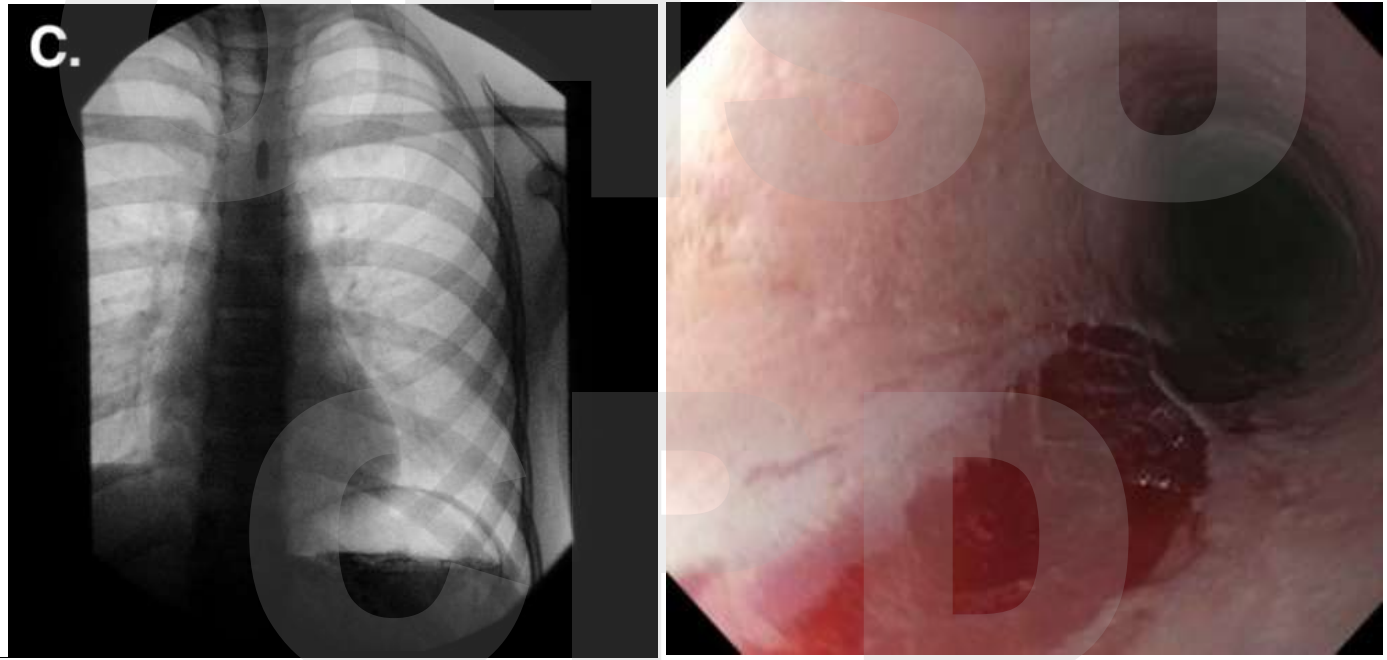
Esophageal Dilation with Mucosal Tear



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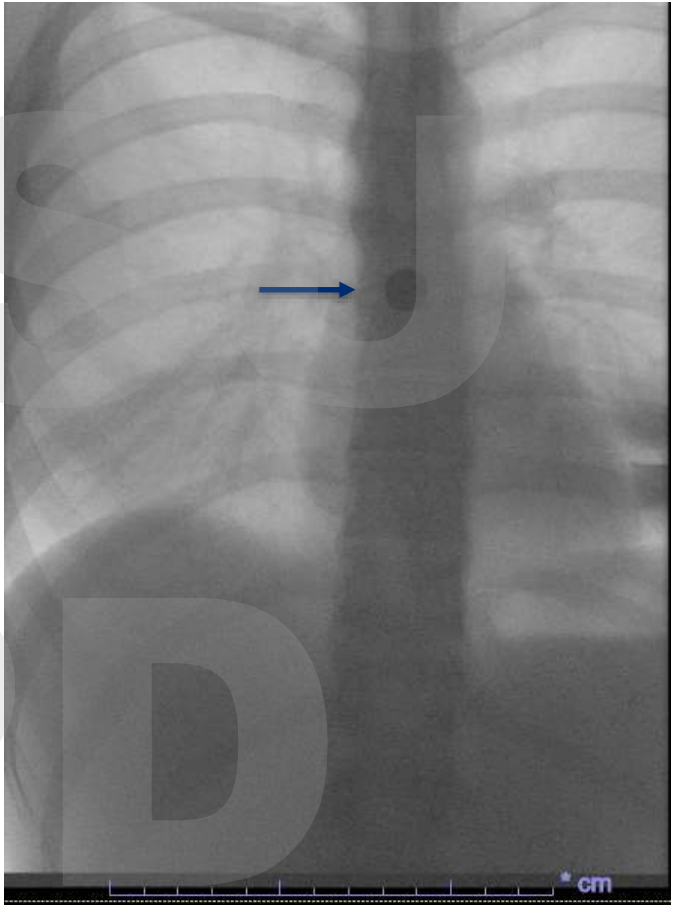
Barium Pill Esophagram

- Addition of a barium pill esophagram allowed detection of clinically relevant esophageal narrowing that was not captured with barium esophagram alone



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The 6 year old “Picky Eater”

- Added dairy, then TNE
- Added egg, then TNE
- Added wheat, then TNE
- Added soy, then TNE
- Food triggers identified: dairy and egg
- Remains off dairy, egg for EoE
- Remains off peanut and tree nut for IgE mediated food allergies

The 17 year old “Fearful Carnivore”

- At follow up, having more food sticking.
- Esophagram with barium pill showed normal caliber esophagus, barium pill hung up for > 5 minutes
- Underwent EGD with esophageal dilation
- Symptoms of food sticking improved

Summary

- The clinical presentation of EoE can vary amongst different age groups and children can develop compensatory behaviors
- Children may present in many different avenues- WCC with Pediatricians, feeding therapy, ENT, pulmonology, allergy.
- If clinical symptoms are suggestive of EoE, consider evaluation by GI for endoscopy
- Future directions include the development of new treatments and methods for disease monitoring in EoE
- Identifying barriers to care and collaboration is key to moving the field forward

Questions?

Children's Hospital Colorado
Here, it's different.

Affiliated with
University of Colorado
Anschutz Medical Campus

Gastrointestinal Eosinophilic Diseases Program

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions including anaphylaxis, serum sickness, angioedema, urticaria, rash, erythema nodosum, and erythema multiforme have occurred. Discontinue DUPIXENT in the event of a hypersensitivity reaction. (5.1)

Conjunctivitis and Keratitis: Advise patients to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination, as appropriate. (5.2)

Eosinophilic Conditions: Be alert to vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.3)

Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of DUPIXENT. Decrease steroids gradually, if appropriate. (5.5)

Arthralgia: Advise patients to report new onset or worsening joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT. (5.7)

Parasitic (Helminth) Infections: Treat pre-existing helminth infections before initiating DUPIXENT. If patients become infected while receiving DUPIXENT and do not respond to anti-helminth treatment, discontinue DUPIXENT until the infection resolves. (5.8)

Vaccinations: Avoid use of live vaccines. (5.9)

ADVERSE REACTIONS

Most common adverse reactions are:

Atopic Dermatitis (incidence ≥1%): injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, dry eye, and eosinophilia. (6.1)

Asthma (incidence ≥1%): injection site reactions, oropharyngeal pain, and eosinophilia. (6.1)

Chronic Rhinosinusitis with Nasal Polyposis (incidence ≥1%): injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis. (6.1)

Eosinophilic Esophagitis (incidence ≥2%): injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections. (6.1)

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