

Eosinophilic Esophagitis: Practical Diagnosis and Management of Pediatric Patients with EoE



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Presented by

Mirna Chehade, MD, MPH

Professor of Pediatrics and Medicine

Director, Mount Sinai Center for Eosinophilic Disorders

Jaffe Food Allergy Institute

Icahn School of Medicine at Mount Sinai



Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

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Faculty Disclosures

Research Support

- ▶ Shire—clinical area: eosinophilic esophagitis
- ▶ Regeneron—clinical area: eosinophilic esophagitis
- ▶ Allakos—clinical area: eosinophilic gastritis

Consultant

- ▶ Shire—clinical area: eosinophilic esophagitis
- ▶ Regeneron—clinical area: eosinophilic esophagitis
- ▶ Allakos—clinical area: eosinophilic gastritis
- ▶ Adare—clinical area: eosinophilic esophagitis

Learning Objectives

- ▶ Recognize the clinical presentation of EoE in infants, toddlers, children and teenagers
- ▶ Explore various dietary and medical management options for pediatric patients with EoE

Module 1

- ▶ Define EoE
- ▶ Discuss etiology
- ▶ Review immunopathogenesis

EoE: Definition

Chronic, immune/antigen-mediated esophageal disease is characterized by

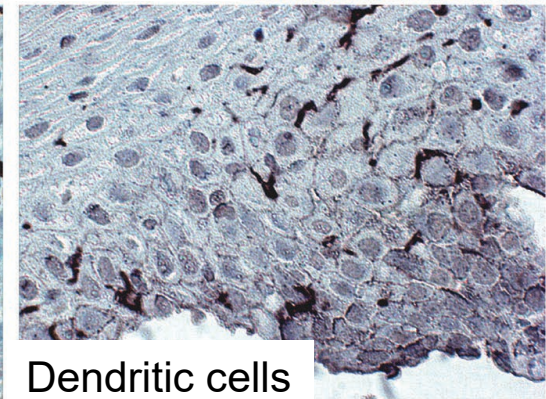
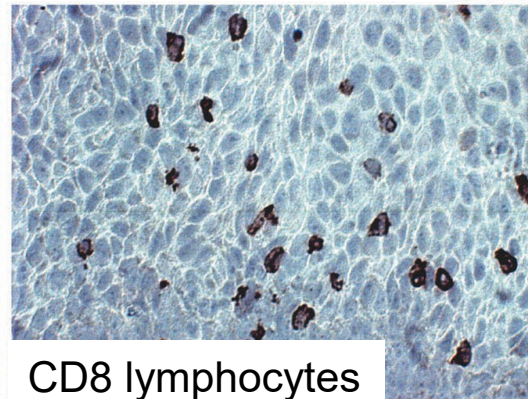
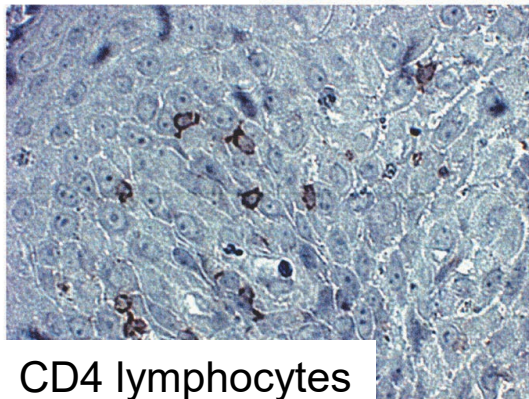
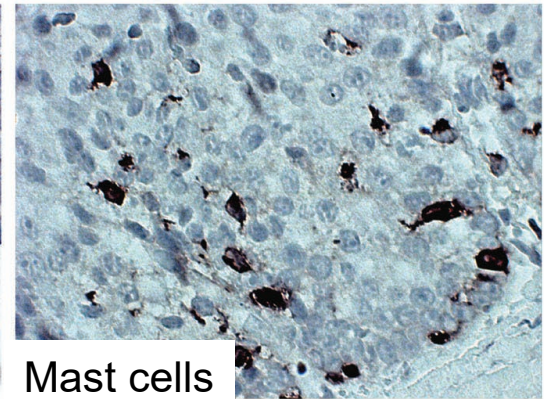
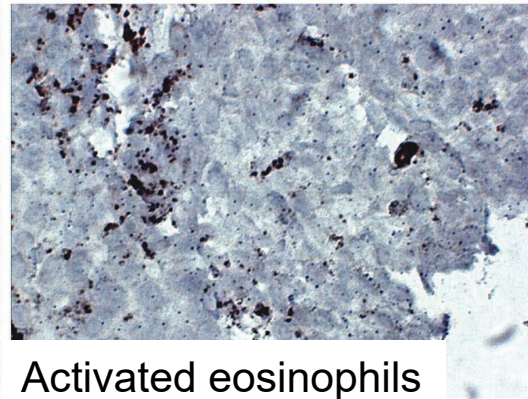
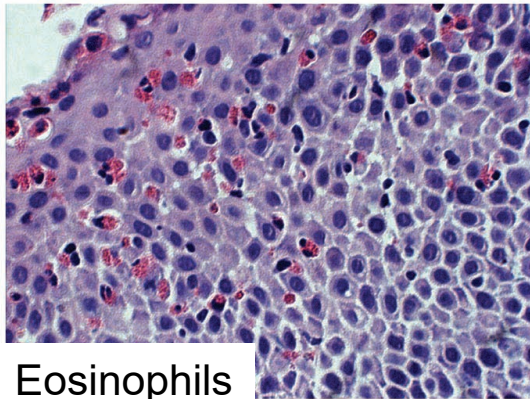
- Clinically: Symptoms related to esophageal dysfunction
- Histologically: Eosinophil-predominant inflammation

EoE: Causes

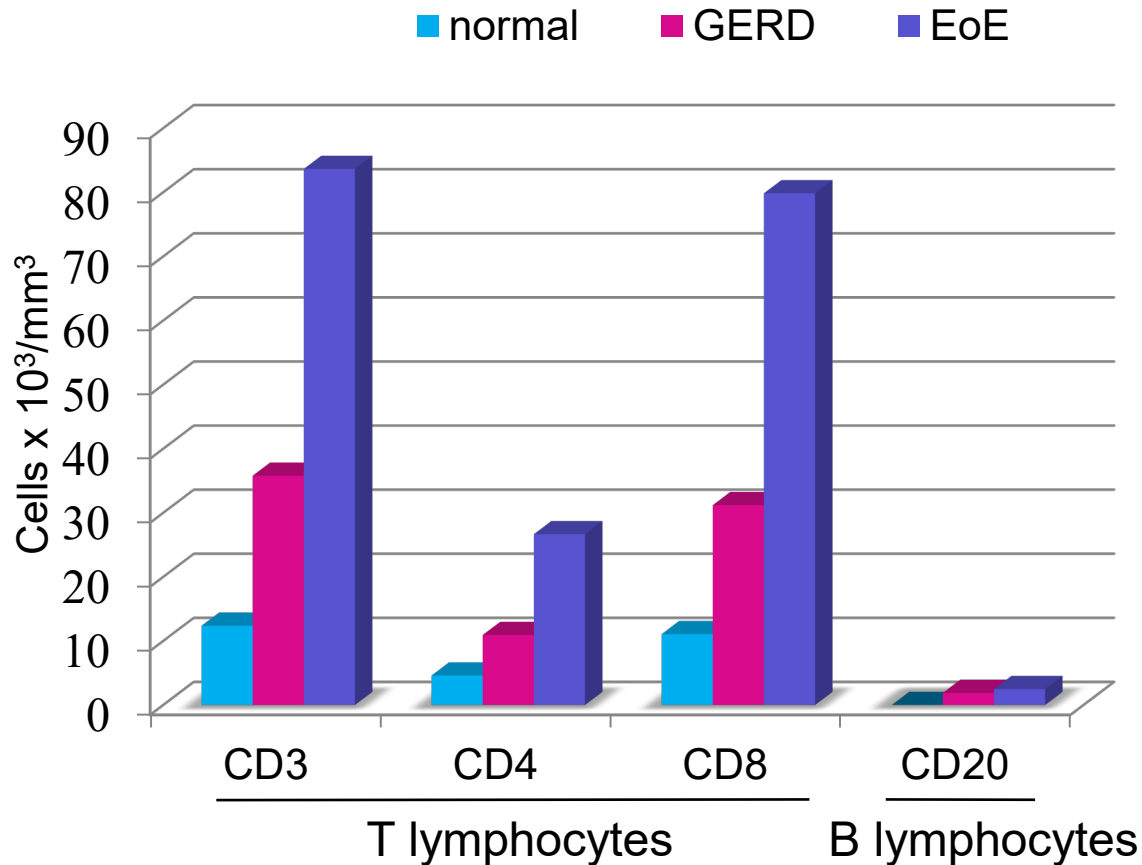
- ▶ EoE triggers
 - Food allergens
 - Environmental allergens

EoE: Allergic Histopathology

Allergen exposure → Allergic inflammatory response → Infiltration of the esophagus with eosinophils and other inflammatory cells



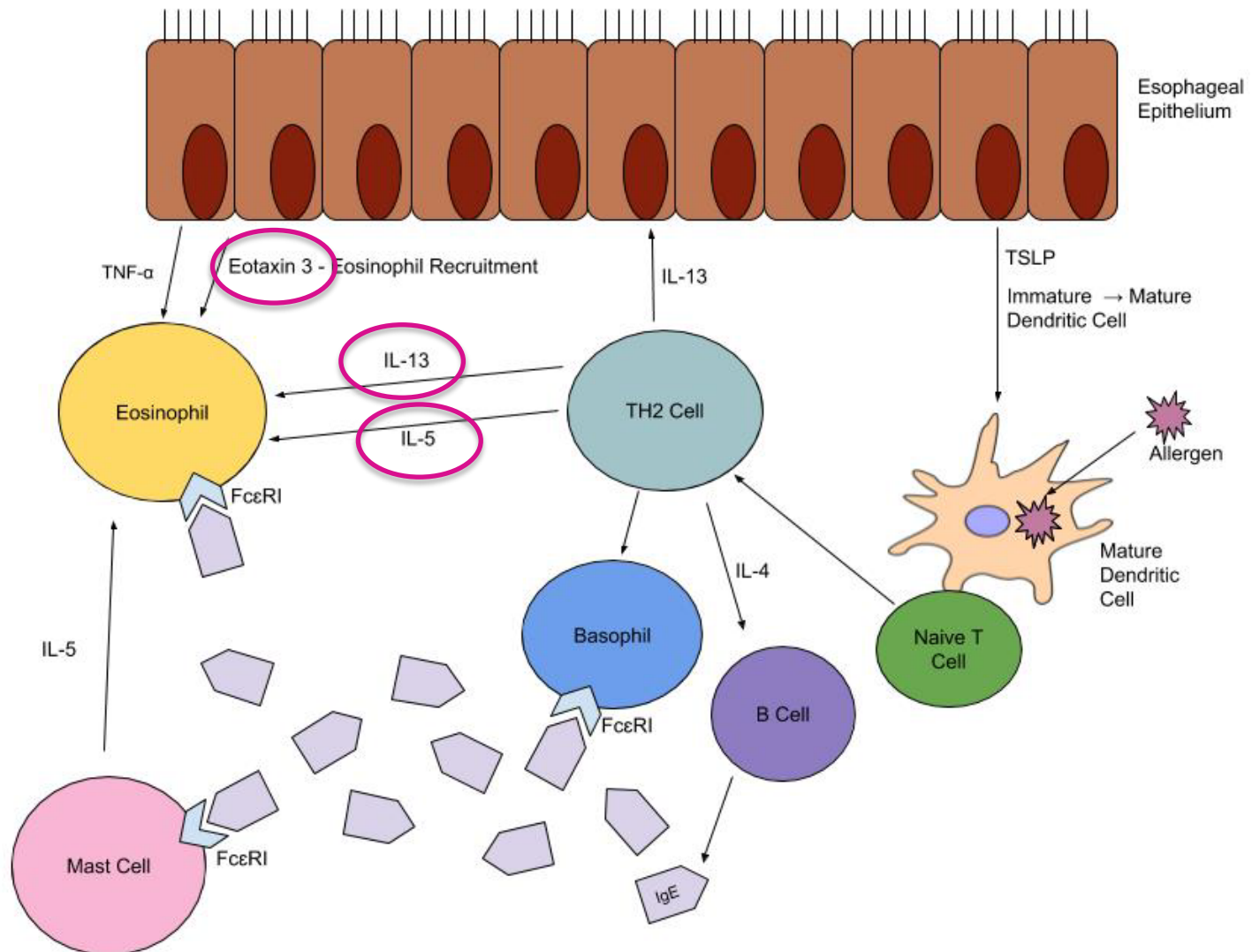
EoE: Allergic Th2 Lymphocytes



Allergic Th2 milieu

- ↑ IL-4
- ↑ IL-13
- ↑ IL-5

EoE: Immunopathogenesis



Module 2

- ▶ Demographics of EoE
- ▶ How to diagnose EoE
- ▶ EoE natural history, if untreated

EoE: Demographics

▶ Age

- Can occur at all ages

▶ Race

- More frequently reported in whites
- Racial minorities likely underdiagnosed

▶ Gender

- More common in males (M:F ratio ~3:1)

▶ Comorbidities

- More common in patients with food allergy
- More common in patients with atopic diseases

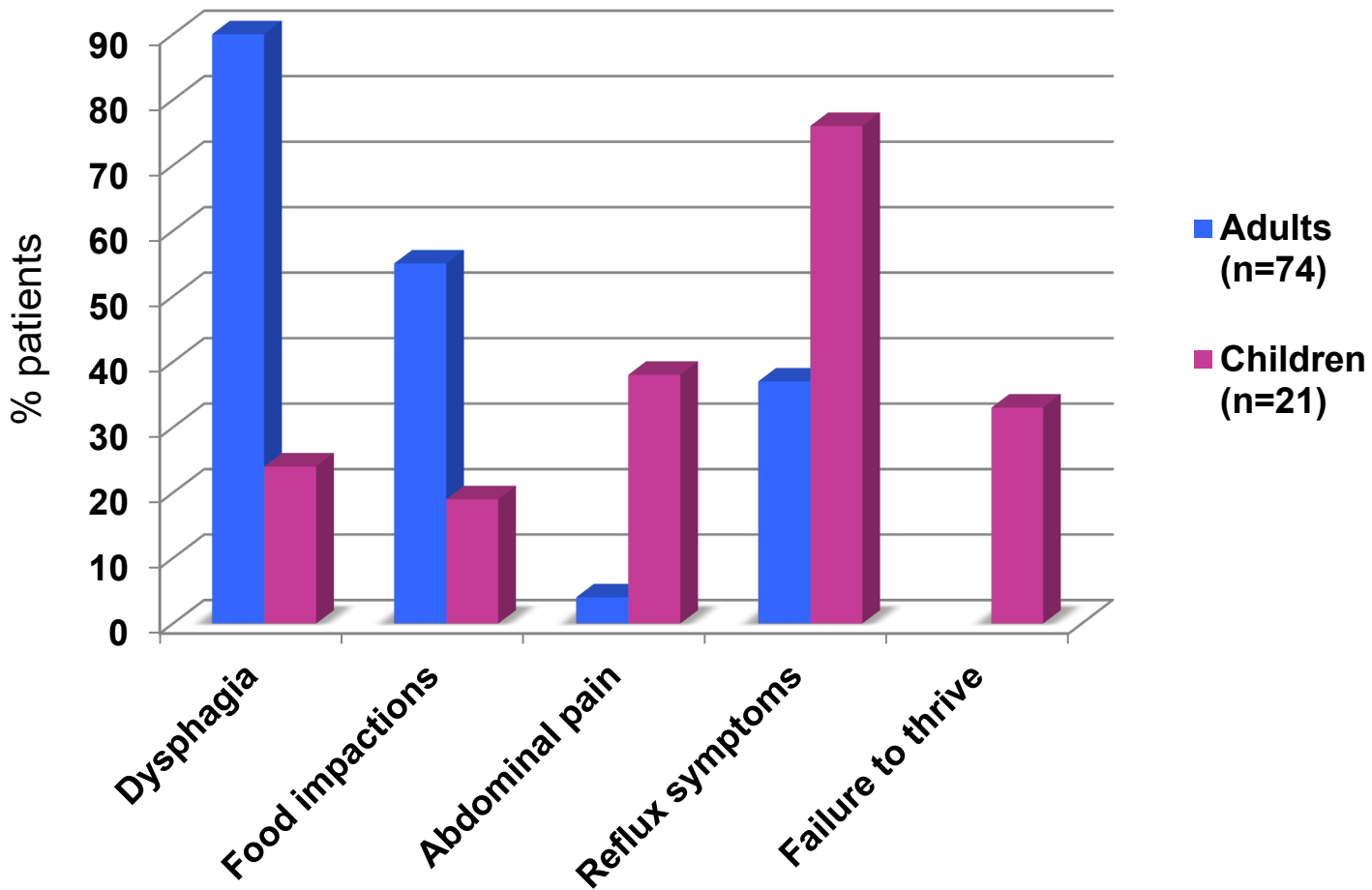
▶ Familial history

- Family history of EoE
- Family history of atopic diseases
- Genetics and shared environment effects

Liacouras et al, J Allergy Clin Immunol 2011
Jensen et al, J Pediatr Gastroenterol Nutr 2013
Chehade et al, J Allergy Clin Immunol Pract 2018

EoE: Diagnosis

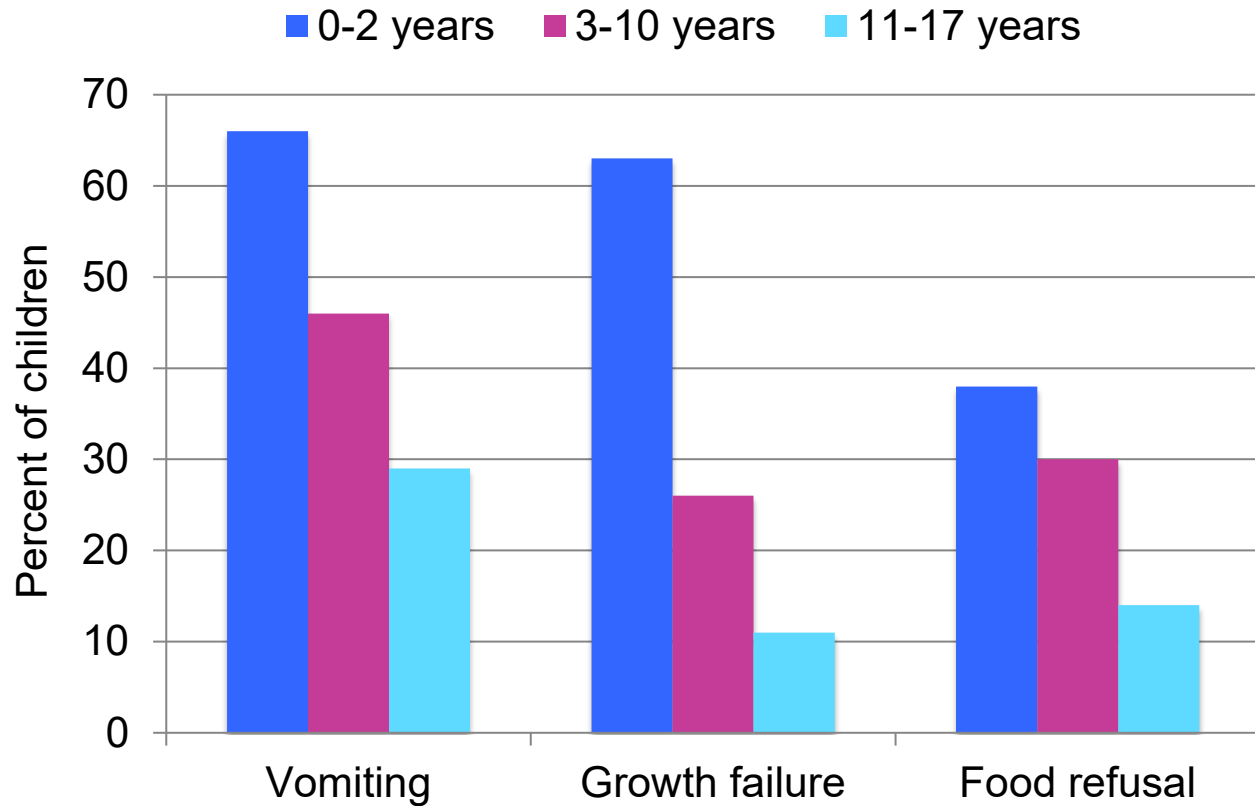
EoE: Symptoms Vary With Age



Chegade et al, J Pediatr Gastroenterol Nutr 2007
Gonsalves et al, Gastrointest Endosc 2006

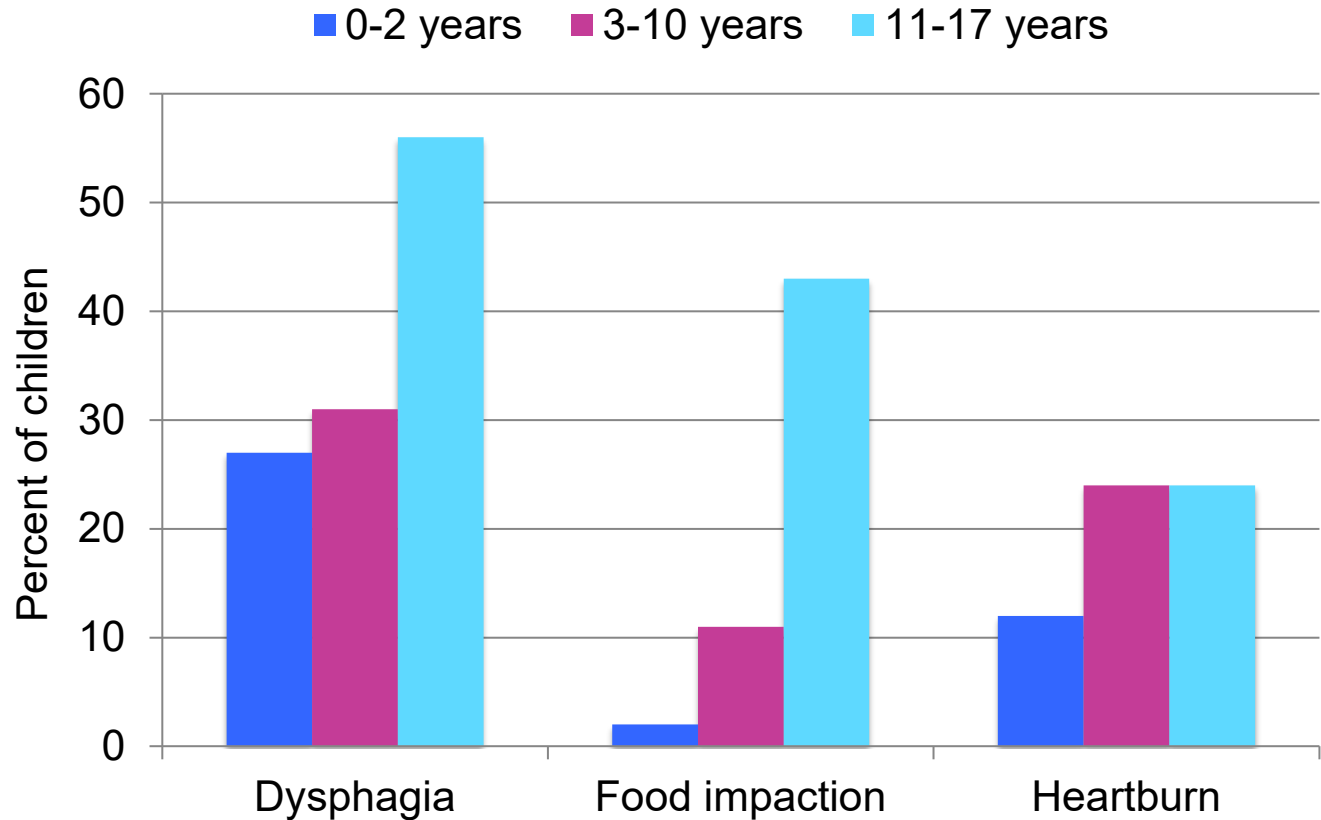
EoE in Children: Comparison of All Symptoms

n=793
476 adults
317 children



EoE in Children: Comparison of All Symptoms

n=793
476 adults
317 children

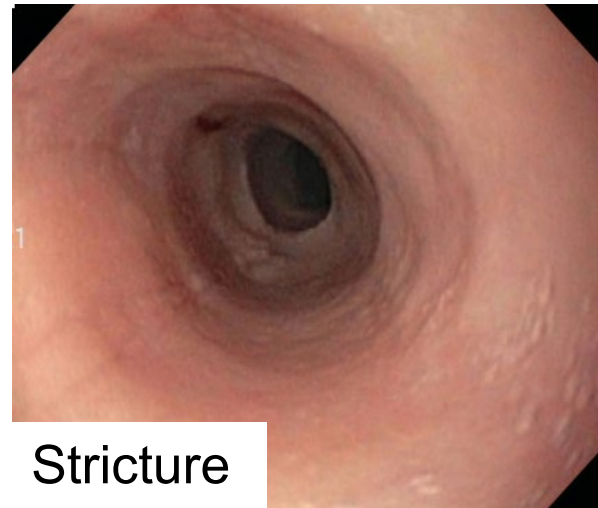
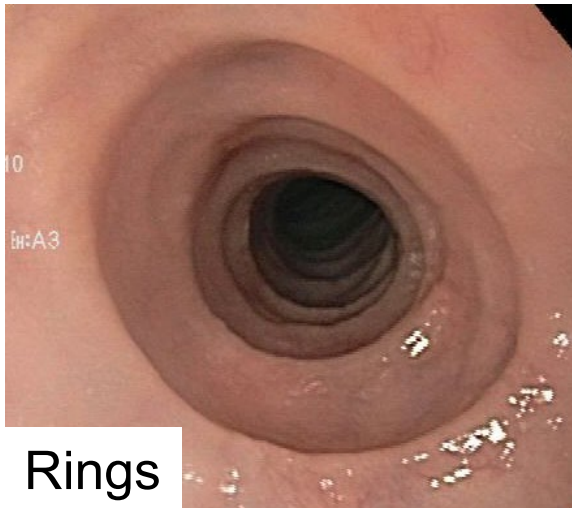
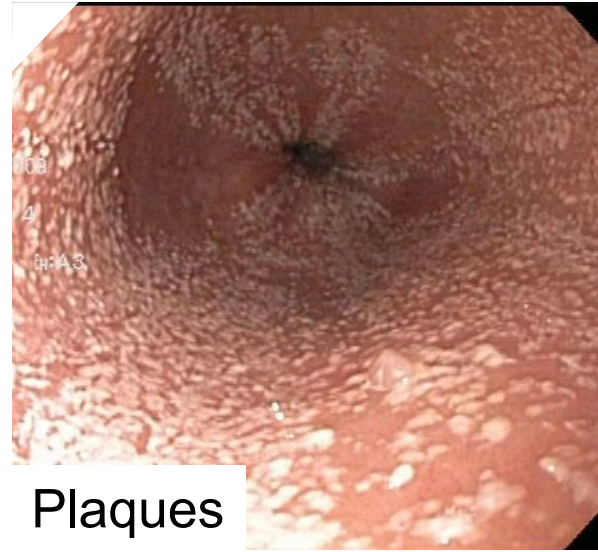
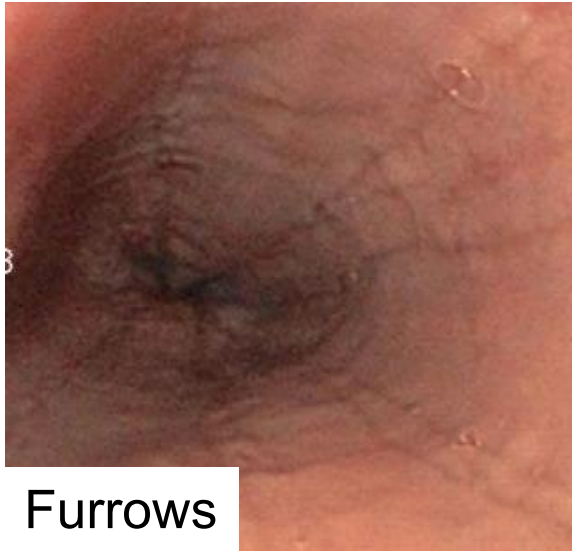


EoE: Challenges in Clinical Presentation

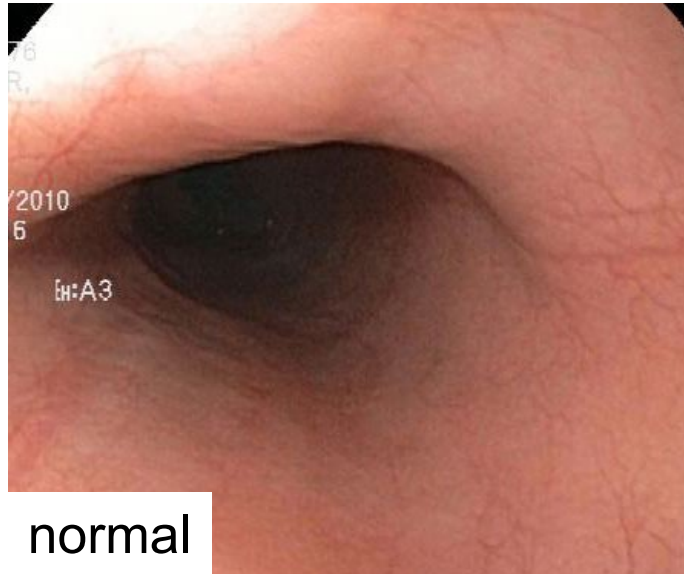
- ▶ **Nonspecific gastrointestinal symptoms → look for:**
 - Early satiety
 - Failure to thrive
 - Personal or family history of food allergy
 - Personal or family history of atopy
 - History of allergic gastrointestinal symptoms in infancy

- ▶ **Subtle symptoms (due to feeding compensatory behaviors) → look for:**
 - Taking too long to finish a meal
 - Prolonged chewing
 - Pocketing food in the mouth
 - Needing to drink with every bite of food
 - Cutting food into very small pieces
 - Lubricating tough/lumpy foods with condiments/dunking in liquids
 - Avoiding tough/lumpy foods altogether
 - Food refusal altogether

EoE: Endoscopic Diagnosis

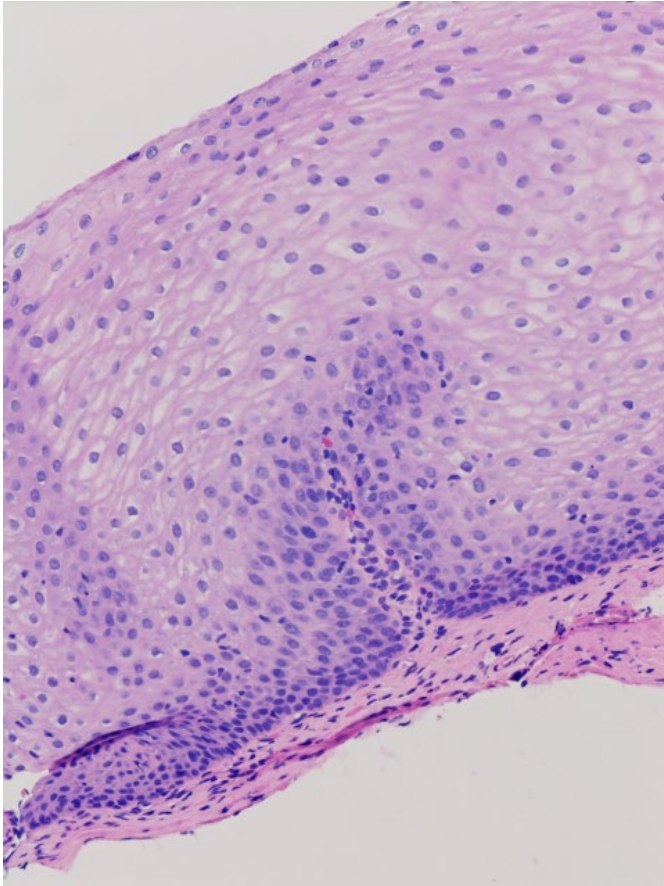


EoE: Endoscopic Diagnosis

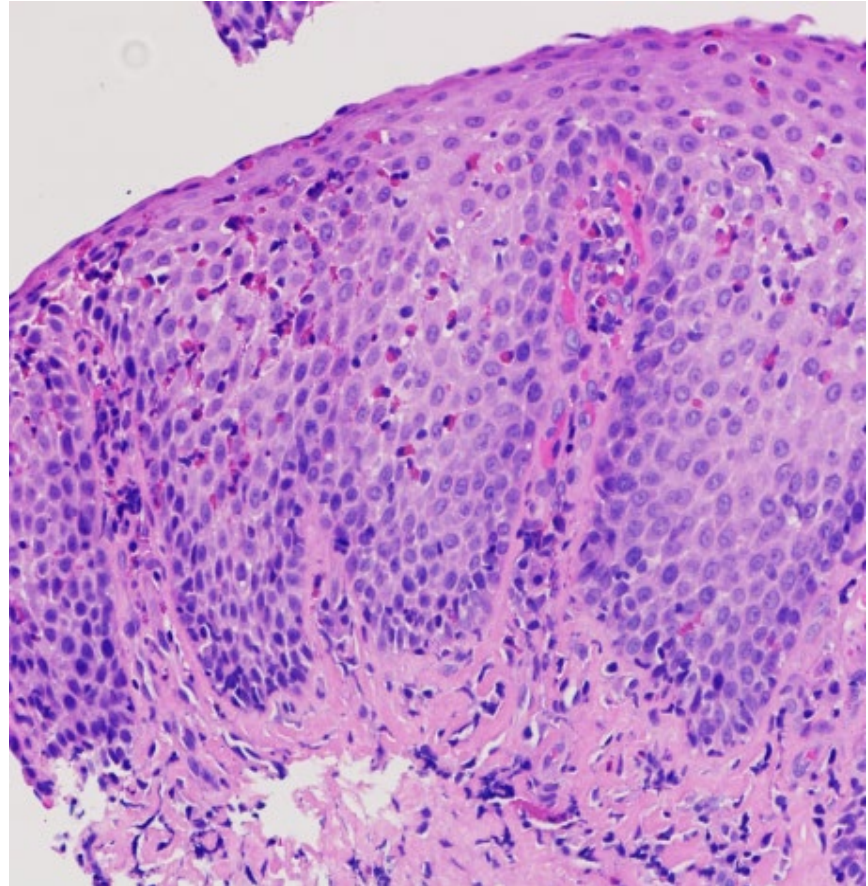


Endoscopy can be normal in up to 20% of patients
→ Biopsies important regardless of the endoscopic findings

EoE: Histological Diagnosis



Normal (0 eos/HPF)

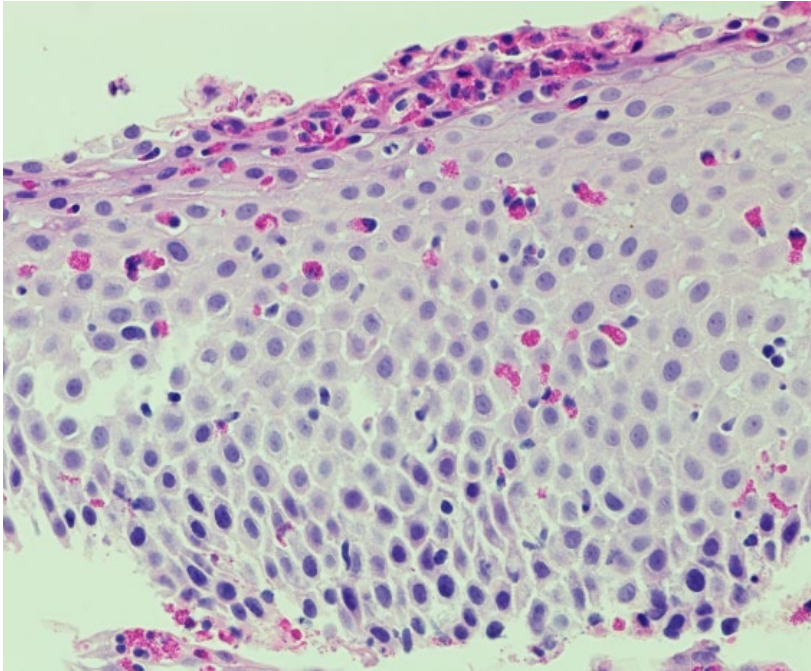


EoE (≥ 15 eos/HPF)

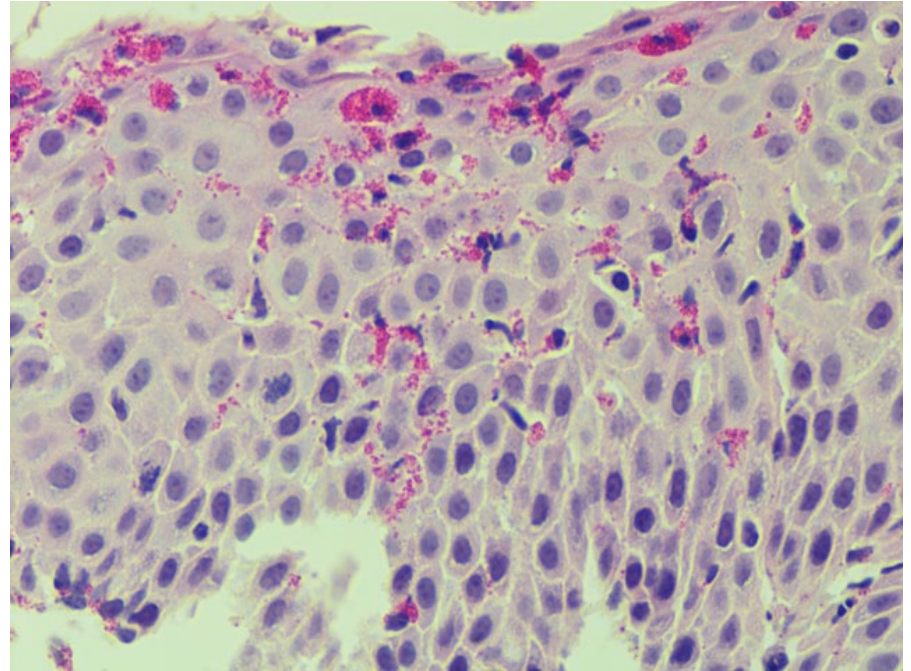
PATCHY DISEASE

eos/hpf, eosinophils per high-power field

EoE: Histological Diagnosis



Eosinophil superficial layering
and microabscesses



Eosinophilic degranulation

EoE: Diagnosis per 2011 Guidelines

- Symptoms
- Esophageal eosinophilia
- Proton pump inhibitor therapy, to rule out PPI-responsive esophageal eosinophilia (PPI-REE)

PPI-REE: Vast Similarities With EoE

- ▶ PPI-REE and EoE indistinguishable clinically, endoscopically, and histologically
- ▶ PPI: anti-inflammatory effect on esophageal epithelial cells *in vitro*
- ▶ Adults with PPI-REE: responded to dietary elimination therapy

Dellon et al, Am J Gastroenterol 2013

Moawad et al, Aliment Pharmacol Ther 2014

Cheng et al, Gut 2013

Sodikoff et al, J Allergy Clin Immunol 2016

Lucendo et al, J Allergy Clin Immunol 2016

Updated 2018 EoE Diagnostic Algorithm

Clinical presentation suggestive of EoE

Upper endoscopy with biopsies

Esophageal eosinophilia (≥ 15 eosinophils/HPF)

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

Eosinophilic esophagitis

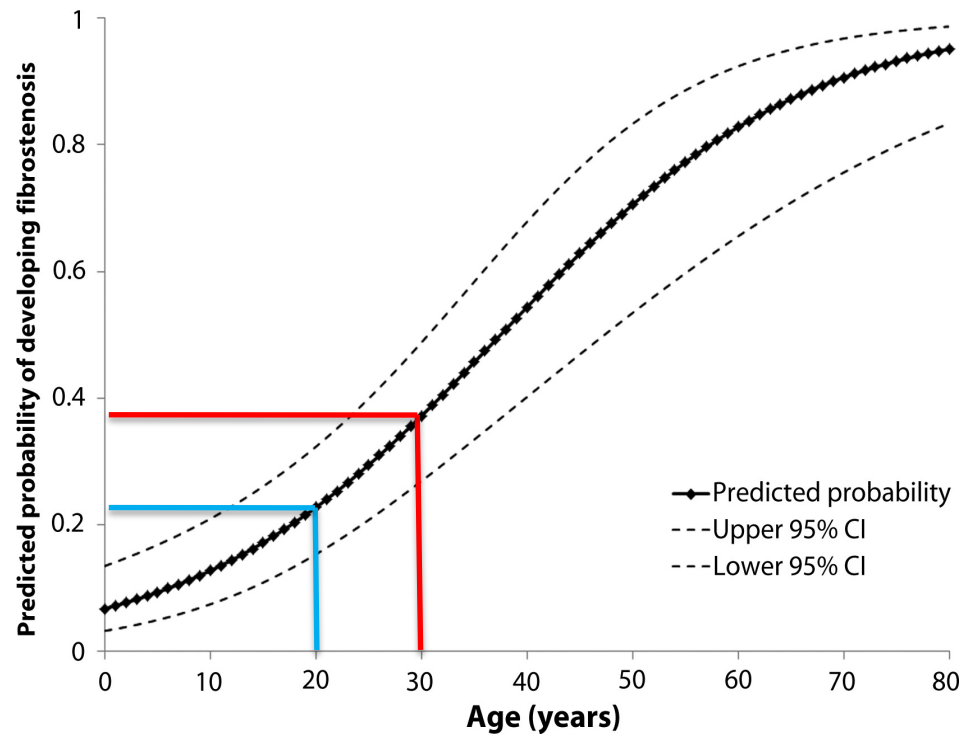
EoE: Natural History

EoE: Natural History

- ▶ EoE is a chronic disease
- ▶ EoE may progress: inflammation-predominant → fibrosis-predominant

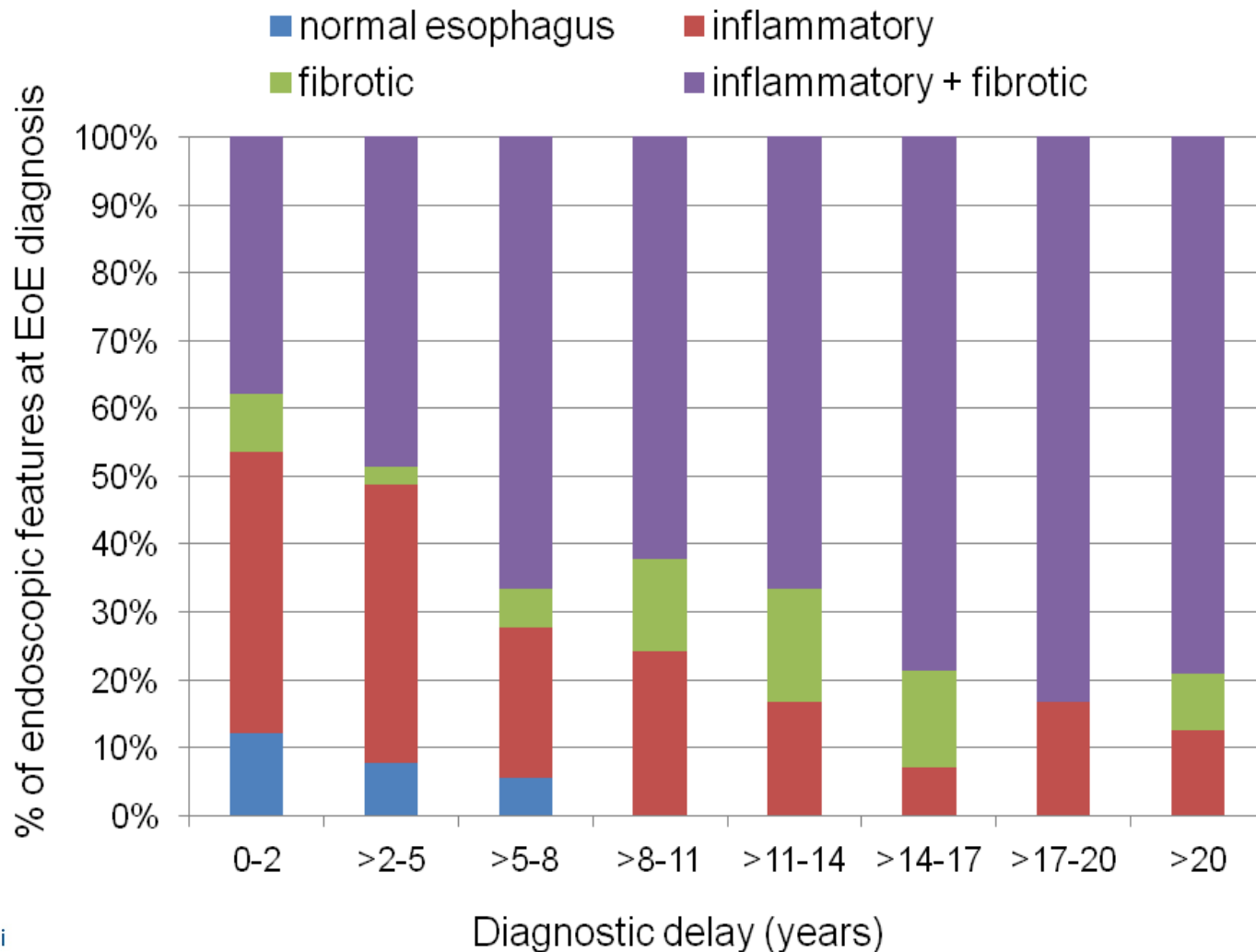
EoE: Course With Increasing Age

North Carolina, 2013
Retrospective
379 children and adults

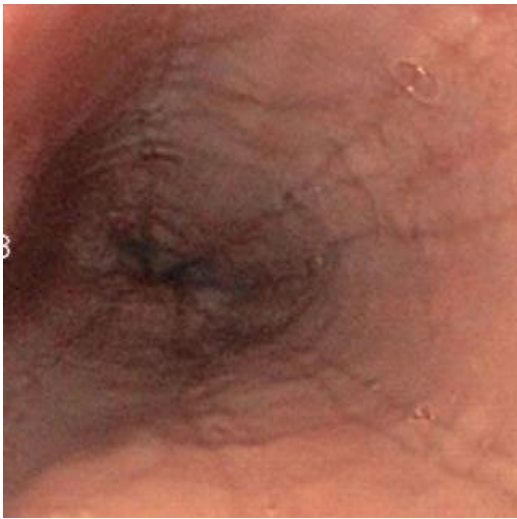


Eosinophilic esophagitis is a progressive fibrostenotic disease

EoE: Course With Increasing Duration of Symptoms



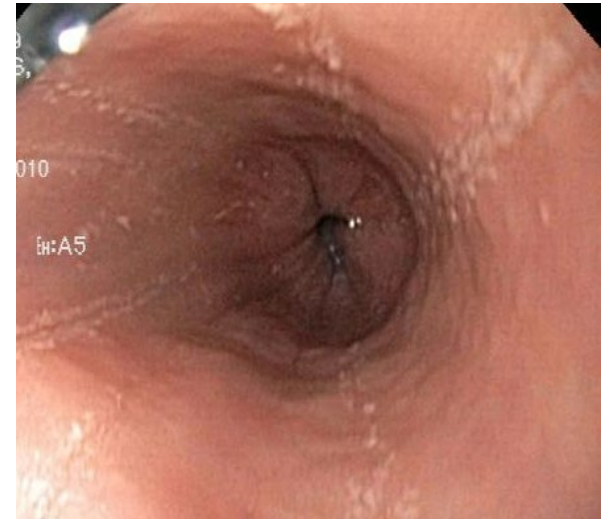
EoE: Inflammatory Phenotype



Furrows



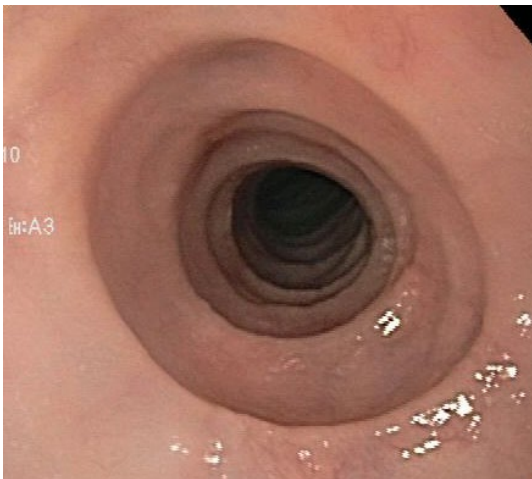
Plaques



Plaques along furrows

- Seen more often in early disease
- Seen more often in children

EoE: Fibrostenotic Phenotype



Rings

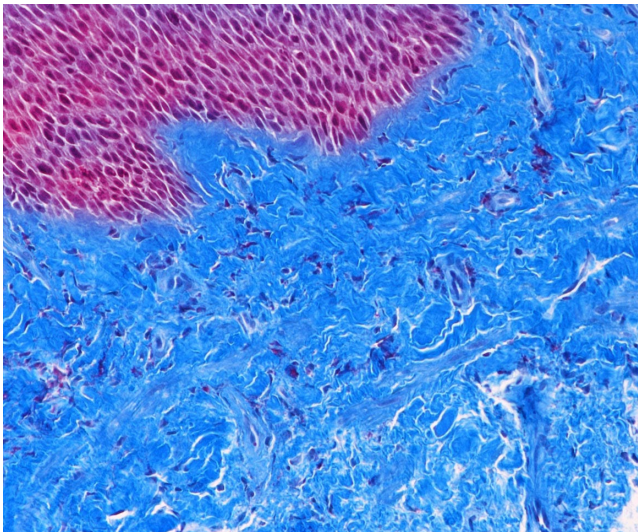


Stricture

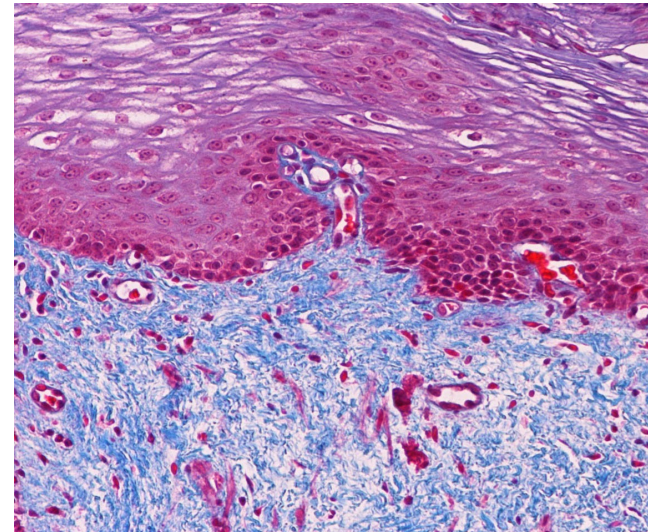
- Seen more often in late disease
- Seen more often in adults

Pediatric EoE: Fibrosis can be reversed with diet or topical corticosteroids

**EoE Patient
Pre-treatment**



**EoE Patient
Post-treatment**



Trichrome stain

Conclusion:

Diagnosis and Natural History of EoE

EoE diagnosis is based on clinical, endoscopic, and histological criteria.

Symptoms can be nonspecific in children with EoE.

If left untreated, EoE can lead to fibrostenotic complications.

Module 3

- ▶ Treatment options
 - Dietary restriction therapies
 - Medications

EoE: Therapy Endpoints

- ▶ Reduce symptoms and esophageal inflammation
- ▶ Reverse existing disease complications
- ▶ Prevent future complications

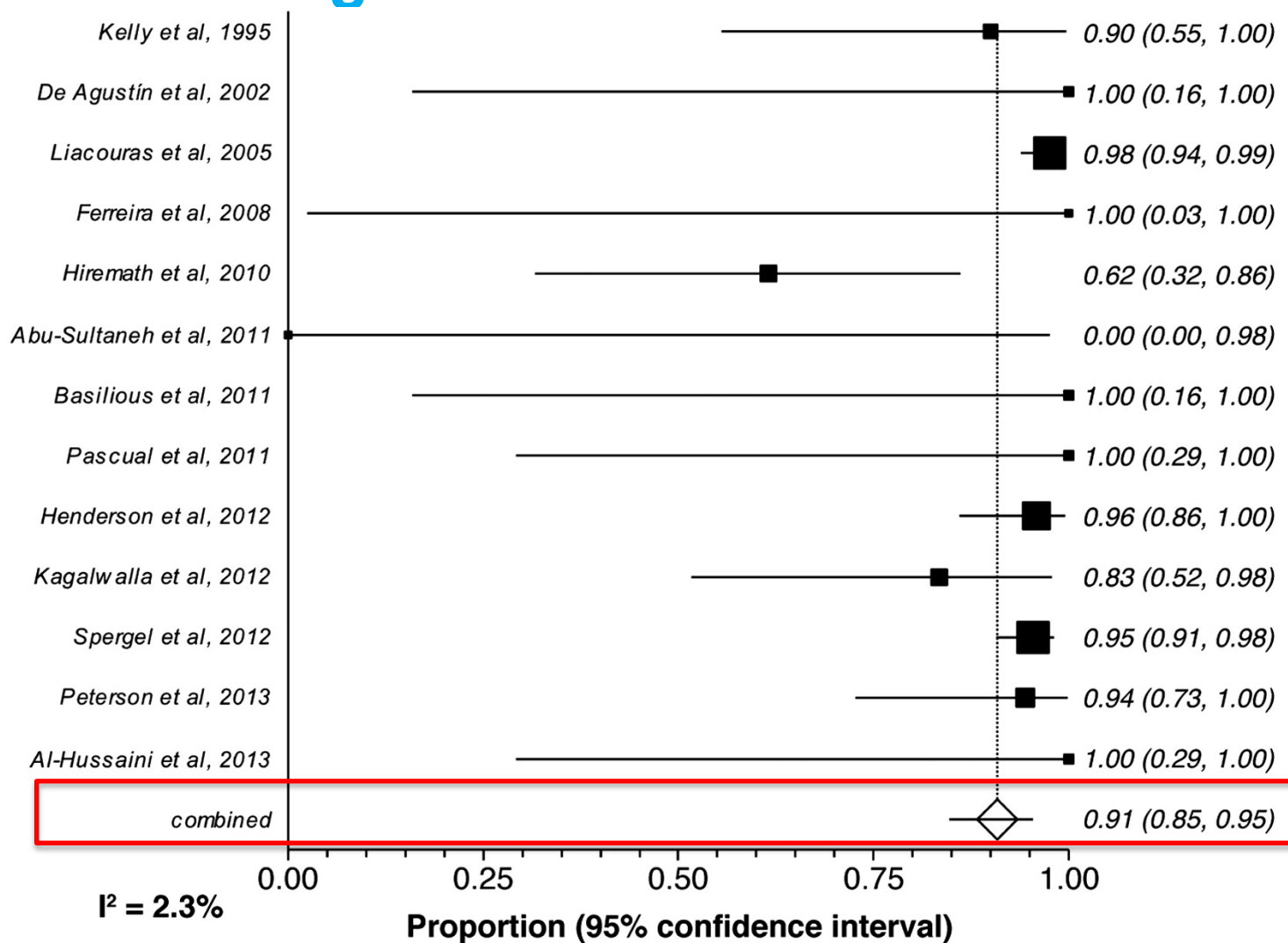
EoE: Commonly Used Therapies

- ▶ Dietary restriction therapies
- ▶ Topical corticosteroid therapies
- ▶ Dilation of esophageal strictures

EoE: Dietary Therapies

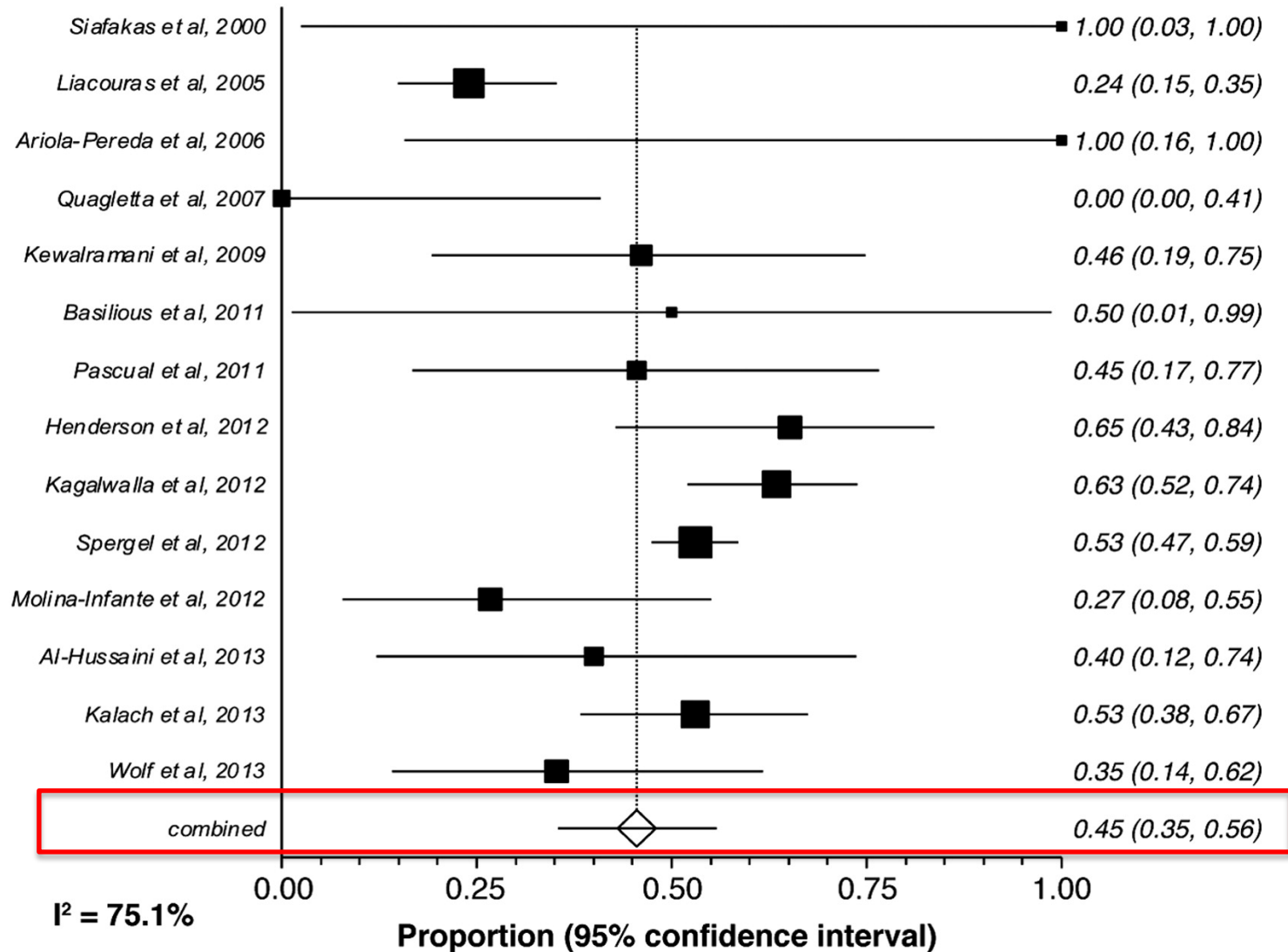
- ▶ **Elemental diet**
 - Amino acid-based formula
 - Amino acid-based formula + 1-2 foods (modified elemental diet)
- ▶ **Test-directed elimination diet**
 - Based on results of skin tests (prick and patch)
- ▶ **Empiric elimination diet**
 - Removal of common food triggers without testing

EoE: Histological remission with elemental diet



Children: 90%, Adults: 94%

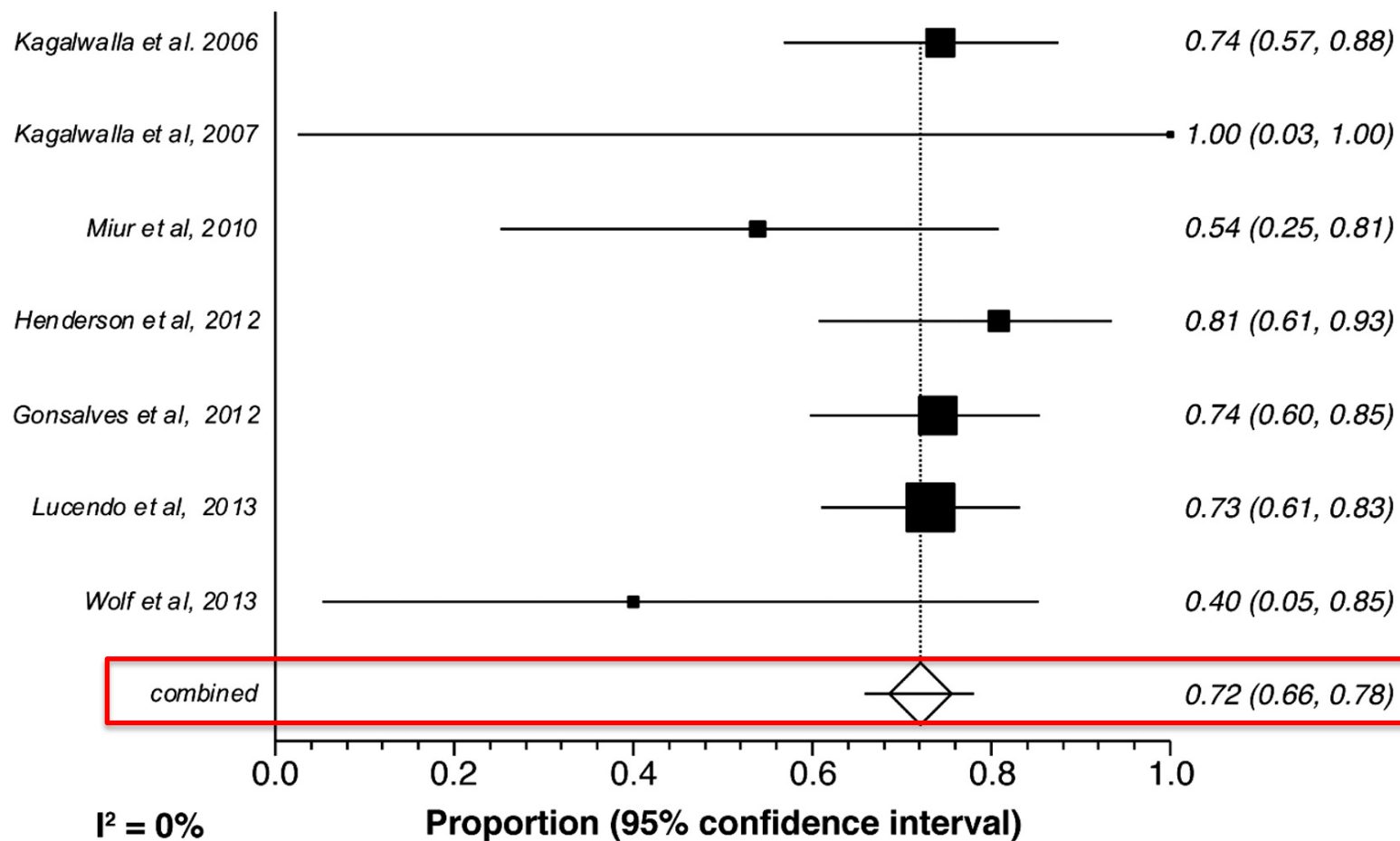
EoE: Histological remission with test-directed diet



Children: 48%, Adults: 32%

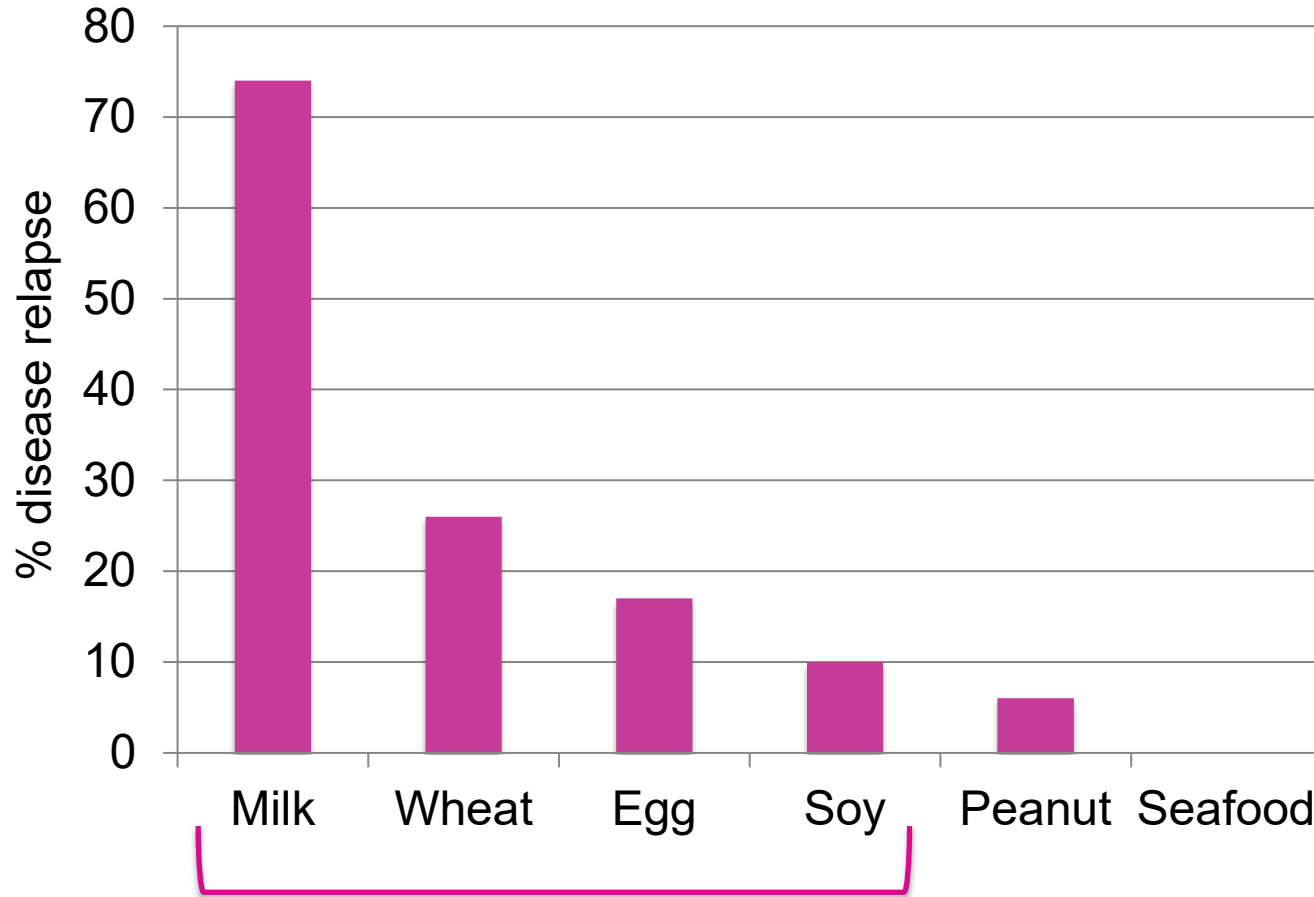
Arias et al, Gastroenterology 2014

EoE: Histological remission 6-food elimination diet



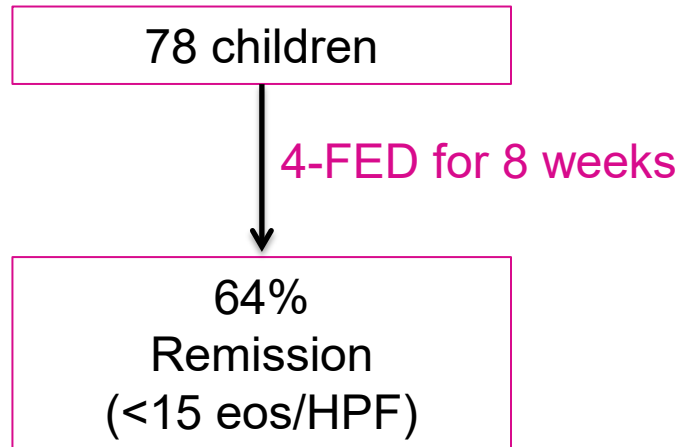
EoE in Children: Common Food Triggers

36 children were rechallenged with foods:



Pediatric EoE: Empiric Elimination Diet (4-FED)

Foods removed:
milk, wheat, egg, soy



Sequential reintroduction of foods, followed by biopsies; triggers identified:

Milk	Wheat	Egg	Soy
85%	33%	35%	19%

EoE: Empiric Elimination Diet

	Remission rate (%) (children)
6-FED	73
4-FED	64
2-FED	43
1-FED	?

Arias et al, Gastroenterology 2014
Kagalwalla...Chehade, Clin Gastroenterol Hepatol 2017
Molina-Infante et al, J Allergy Clin Immunol 2017

EoE: Current Diets Under Study in Children

1-FED versus 4-FED:

Elimination of milk VERSUS milk, wheat, egg, soy
(*ClinicalTrials.gov NCT02610816*)

Dietary Restrictions

Pros

Some diets are highly effective

Allow potential identification of food triggers

Prevent need for chronic medications, with their potential side effects

May reduce systemic inflammation (vs local effect of medications)

Cons

Require a large effort by the patient and family for implementation

Most diets require availability of a specialized dietitian

Multiple endoscopies needed to identify the food trigger

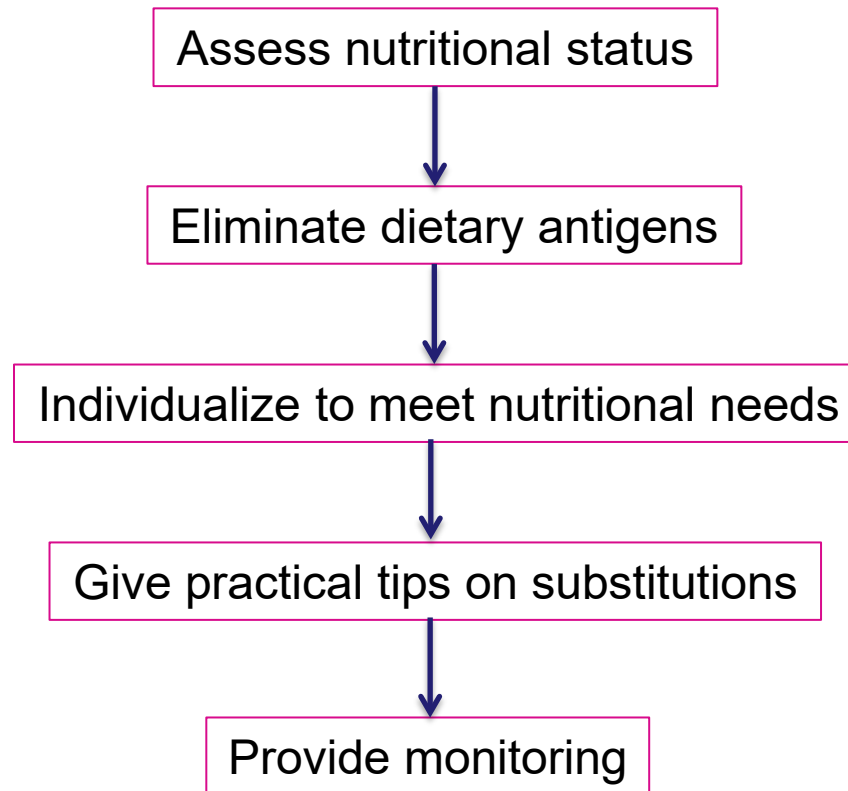
Not effective when environmental allergens trigger EoE

EoE: Which children should get dietary therapy?

- ▶ Patients are selected based on a discussion with the family.
- ▶ Multiple factors are considered before opting for dietary therapy and choosing type of dietary therapy:
 - Age
 - Nutritional status
 - Feeding difficulties
 - Self-restrictive behaviors towards foods
 - Social settings
 - Motivation of patient and family
 - Social support system
 - Financial support system
 - Acceptance of multiple endoscopies

EoE: Nutritional Management in Practice

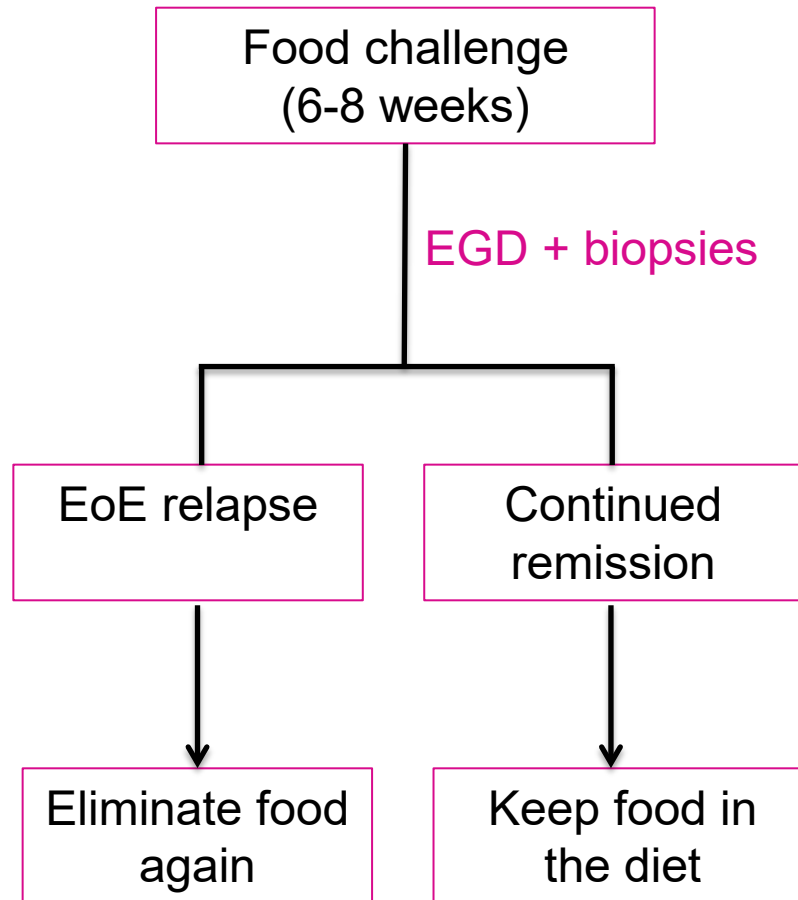
Work Group Report of AAAAI 2017 for dietary therapy implementation:



EoE: Dietary Therapy as Maintenance Therapy?

- Diets can be gradually liberalized over time, reintroducing foods that do not trigger EoE.
- Challenges with food introductions:
 - Difficulty identifying safe foods (mostly trial and error)
 - Rare chance of *de novo* acute allergic reactivity → SPT/serum food-IgE level (by an allergist) may be needed before food reintroduction

EoE: Commonly Used Food Challenge Algorithm



Conclusion: Dietary Therapy for EoE

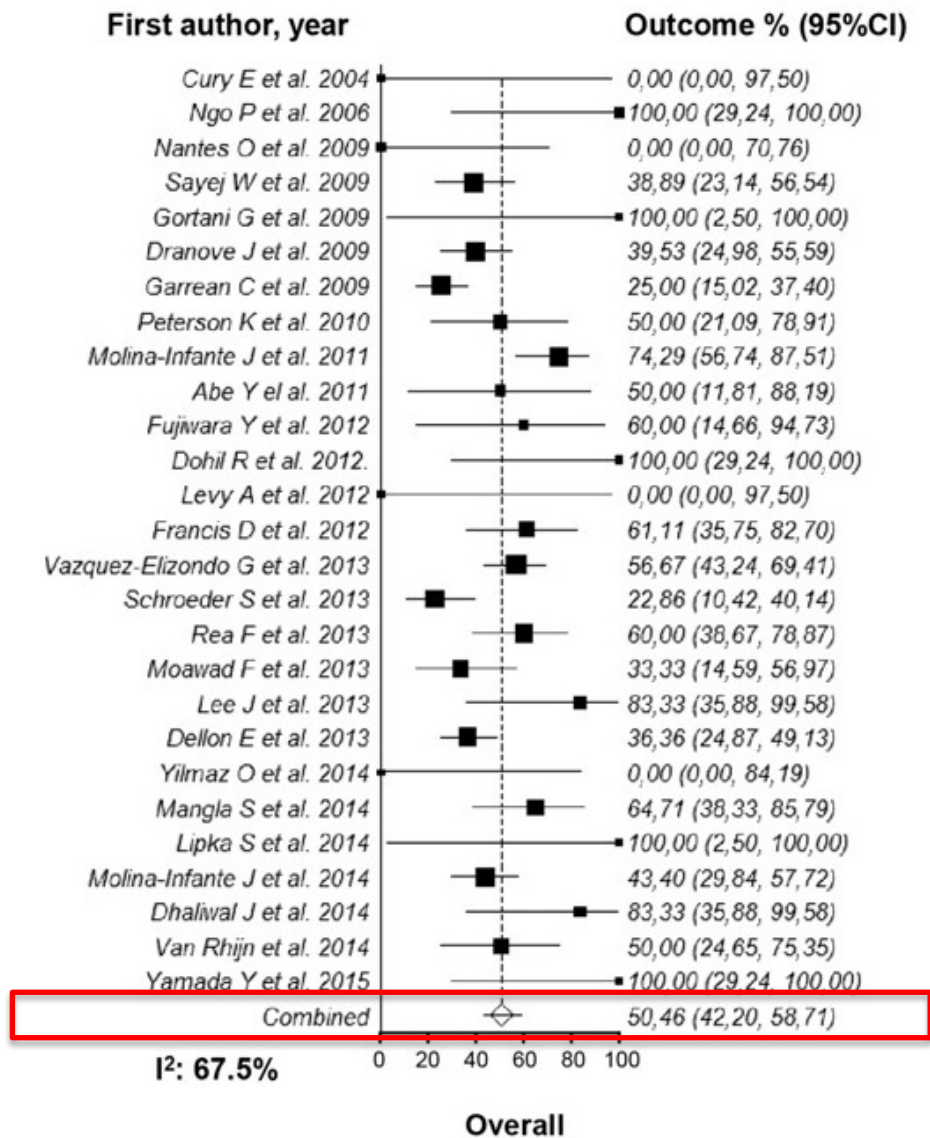
Dietary therapy can be effective.

It is optimal for eligible and motivated patients.

Ongoing support is needed for its success.

EoE: Medical Therapy

EoE: Histological remission with proton pump inhibitors



Children: 54%, Adults: 50%

Lucendo et al, Clin Gastroenterol Hepatol 2016

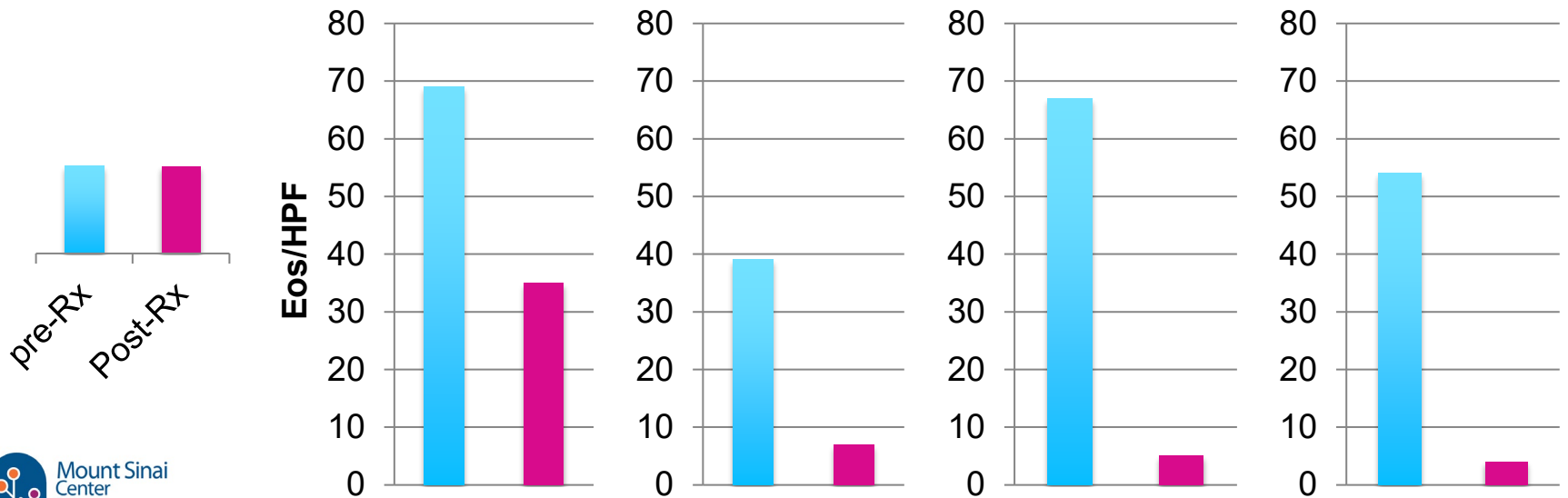
EoE: Topical Corticosteroids

- ▶ Commonly used formulations:
 - Fluticasone to swallow
 - Viscous budesonide to swallow

None are FDA approved to be swallowed for EoE.

EoE: Histological response to topical corticosteroids in children

RCT	Konikoff Gastro 2006	Schaefer CGH 2008	Dohil Gastro 2010	Butz Gastro 2014
No. subjects	36	80	24	42
Drug	fluticasone	fluticasone	budesonide	fluticasone
µg/day	880	880/1760	1000/2000	1760
Control group	placebo	prednisone	placebo	placebo
Blinding	DB	open	DB	DB
Rx duration	12 weeks	4 weeks	12 weeks	12 weeks



DB, double-blind

EoE: 2011 Guidelines Recommendations

Recommended doses of topical corticosteroids in children

- Fluticasone
 - Children: 88–440 mcg 2 to 4 times daily
- Budesonide
 - Children <10 years: 1 mg daily
 - Older children: 2 mg daily

Very wide dose ranges; effective doses not yet established

EoE: Current Topical Corticosteroids Under Study in Children

Oral budesonide suspension:

Phase 3 trial + extension, teenagers and adults

(*ClinicalTrials.gov*: NCT02605837, NCT02736409)

Course Update (Nov-2022):

NCT02605837 results now published:

Budesonide oral suspension 2 mg twice daily was superior to placebo in improving histologic, symptomatic and endoscopic outcomes over 12 weeks.

<https://pubmed.ncbi.nlm.nih.gov/33887475/>

NCT02736409 results now published:

For full responders to induction therapy, continuing budesonide oral suspension numerically improved maintenance of efficacy vs. withdrawal..

<https://pubmed.ncbi.nlm.nih.gov/34182150/>

Topical Corticosteroids

Pros

Some formulations highly effective

Allow ingestion of EoE food triggers

Improve quality of life for patients with EoE

Cons

Need for medication on a daily basis

Potential for topical side effects (eg, local candidal infection)

Potential for systemic side effects (eg, adrenal suppression)

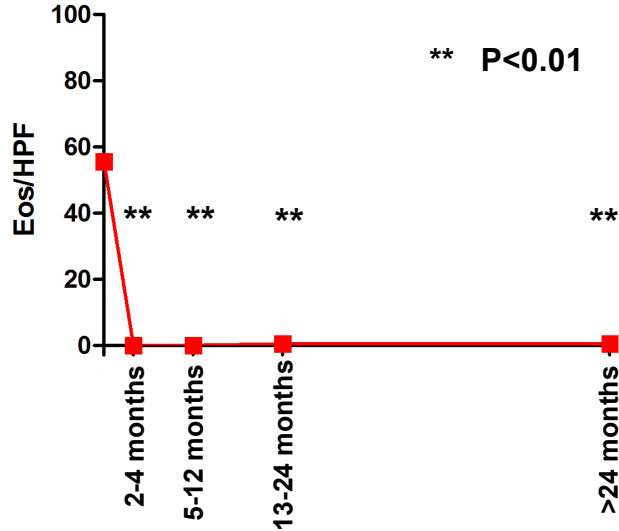
EoE: Which Children Should Get Medications?

- ▶ Patients are selected based on a discussion with the family
- ▶ Factors to consider before opting for medications
 - Age
 - Social settings
 - Motivation of patient and family
 - Social support system
 - Financial support system
 - When dietary therapy proves unsuccessful or too difficult to implement/continue

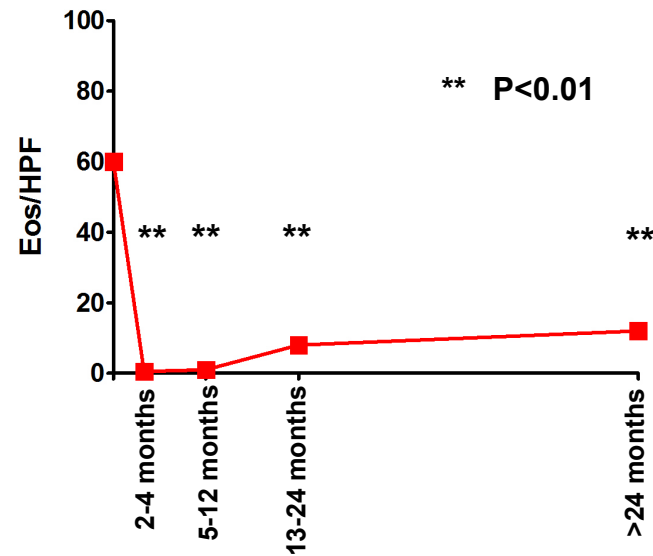
Topical Steroids as Maintenance Therapy?

- ▶ EoE relapses once topical steroids are discontinued
- ▶ Effectiveness for long-term use not well studied
 - Children: effective in prospective study up to 5.5 years

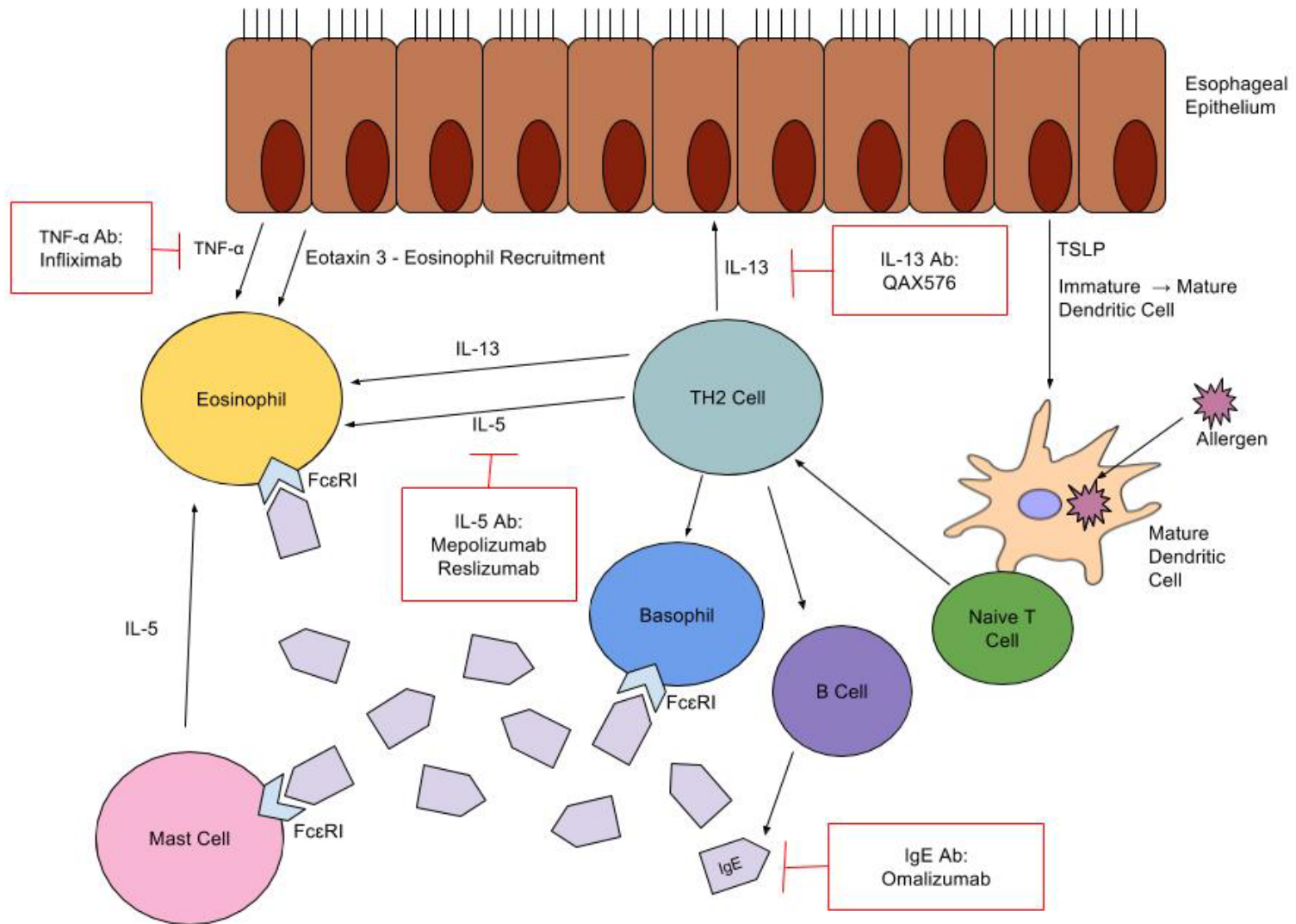
Proximal Esophagus



Distal Esophagus



EoE: Biologics



EoE: Current Biologics Under Study

- ▶ None currently for children
- ▶ Anti-IL-13 in adults
 - RPC4046: Possible histological and clinical improvement in steroid-refractory patients (*ClinicalTrials.gov* NCT02098473)
- ▶ Anti-IL-4R in adults
 - Possible histological and clinical improvement in atopic patients (*ClinicalTrials.gov* NCT02379052)

Course Update (Nov-2022):

anti-IL-4R (dupilumab) was recently FDA-approved (May 2022) for adolescents and adults with EoE

Conclusion: Medications for EoE

None are FDA-approved to date.

Chronic therapy is needed.

Course Update (Nov-2022):

One drug (dupilumab) so far approved by the FDA

EoE: Key Takeaways

- ▶ EoE is a chronic disease.
- ▶ Untreated EoE can lead to fibrostenotic complications.
- ▶ Early recognition and referral are important.
- ▶ Diagnosis is based on clinical, endoscopic, and histological criteria.
- ▶ Long-term therapy for EoE (diets or medications) is essential to prevent complications.
- ▶ Ongoing involvement of pediatrician, pediatric gastroenterologist, allergist, and dietitian result in the best outcomes.



mirna.chehade@mssm.edu