

# 2019 Southeastern Pediatric Nutrition Conference

November 14th, 2019

## **E**osinophilic **E**sophagitis: The Many Pitfalls in Diagnosis and Management: PPIs, Endoscopy, Drugs, Diet and Beyond

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**Children's Hospital Colorado**  
**University of Colorado School of Medicine**





# Disclosures

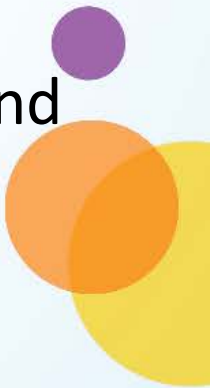
- **Dan Atkins MD**

- Financial:

- Dr. Atkins is an Associate Professor in the Department of Pediatrics at the University of Colorado School of Medicine, where he receives a salary.
    - University of Colorado School of Medicine – salary
    - Receives a consulting fee from Allakos


- Non-Financial:

- Fellow of the American Academy of Allergy, Asthma and Immunology (AAAAI); Chair of the Eosinophilic Gastrointestinal Diseases Committee of the AAAAI





# Session Objectives

1. Describe the symptoms, clinical presentation, endoscopic and pathological findings associated with eosinophil esophagitis.
  2. Outline a practical approach to the evaluation of patients with suspected eosinophilic esophagitis.
  3. Review the treatment options for managing eosinophilic esophagitis.
  4. Contrast the efficacy, benefits, barriers and implementation of the different dietary approaches to the management of eosinophilic esophagitis.
- 



# Case History

- 3 year old boy with eczema, peanut allergy, and asthma who is not growing well
- Picky, slow eater with poor appetite and a self-restricted diet
- Would rather drink than eat, won't eat meats or breads
- Occasionally chokes, gags and vomits while eating
- Won't try new foods
- Endoscopy reveals esophageal eosinophilic inflammation.



# Eosinophilic Esophagitis (EoE)

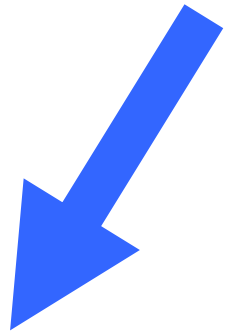
**“Eosinophilic esophagitis represents a chronic, immune/antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.”**





# Diagnostic Guidelines

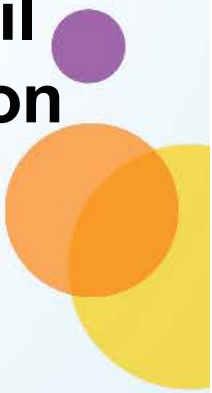
**EoE is a clinico-pathologic disease**



**Characterized by  
symptoms related to  
esophageal dysfunction**



**1 or more esophageal  
biopsies show eosinophil  
predominant inflammation  
(15+ eos in peak hpf)**





# Diagnostic Guidelines

EoE is a *clinico-pathological* disease defined by

- Symptoms of esophageal dysfunction
- Esophageal biopsy specimen with eosinophil-predominant inflammation ( $\geq 15$  eos/400Xhpf)
- Disease isolated to the esophagus & other causes excluded (**PPI-responsive esophageal eosinophilia**)
- Remission of disease with dietary exclusion, topical corticosteroids, or both
- Diagnosed by taking all clinical and pathological information into consideration



# 2014: Tissue biomarkers of PPI-REE and EoE are similar

Clinical Gastroenterology and Hepatology 2014;12:2015–2022

## Markers of Eosinophilic Inflammation for Diagnosis of Eosinophilic Esophagitis and Proton Pump Inhibitor–Responsive Esophageal Eosinophilia: A Prospective Study



Evan S. Dellon,<sup>\*,‡</sup> Olga Speck,<sup>§</sup> Kimberly Woodward,<sup>§</sup> Shannon Covey,<sup>§</sup> Spencer Rusin,<sup>§</sup> Jessica H. Gebhart,<sup>\*</sup> Xiaoxin Chen,<sup>‡,||</sup> John T. Woosley,<sup>§</sup> and Nicholas J. Shaheen<sup>\*,‡</sup>





Major basic protein

Eotaxin-3

Tryptase

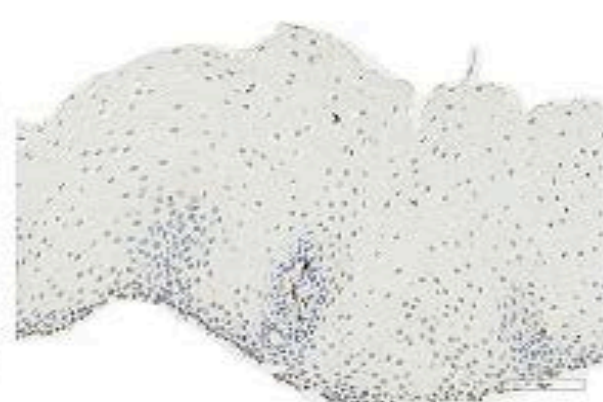
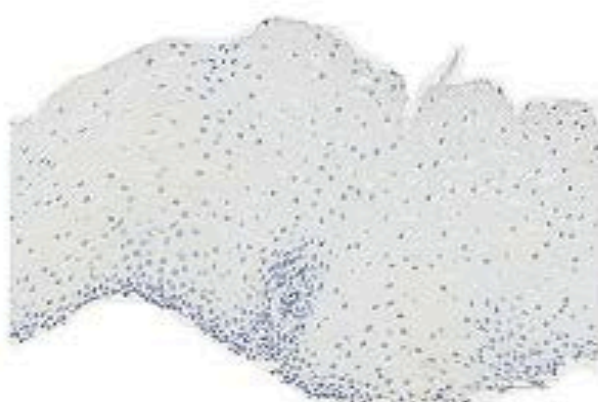
PPI-REE



EoE



Control

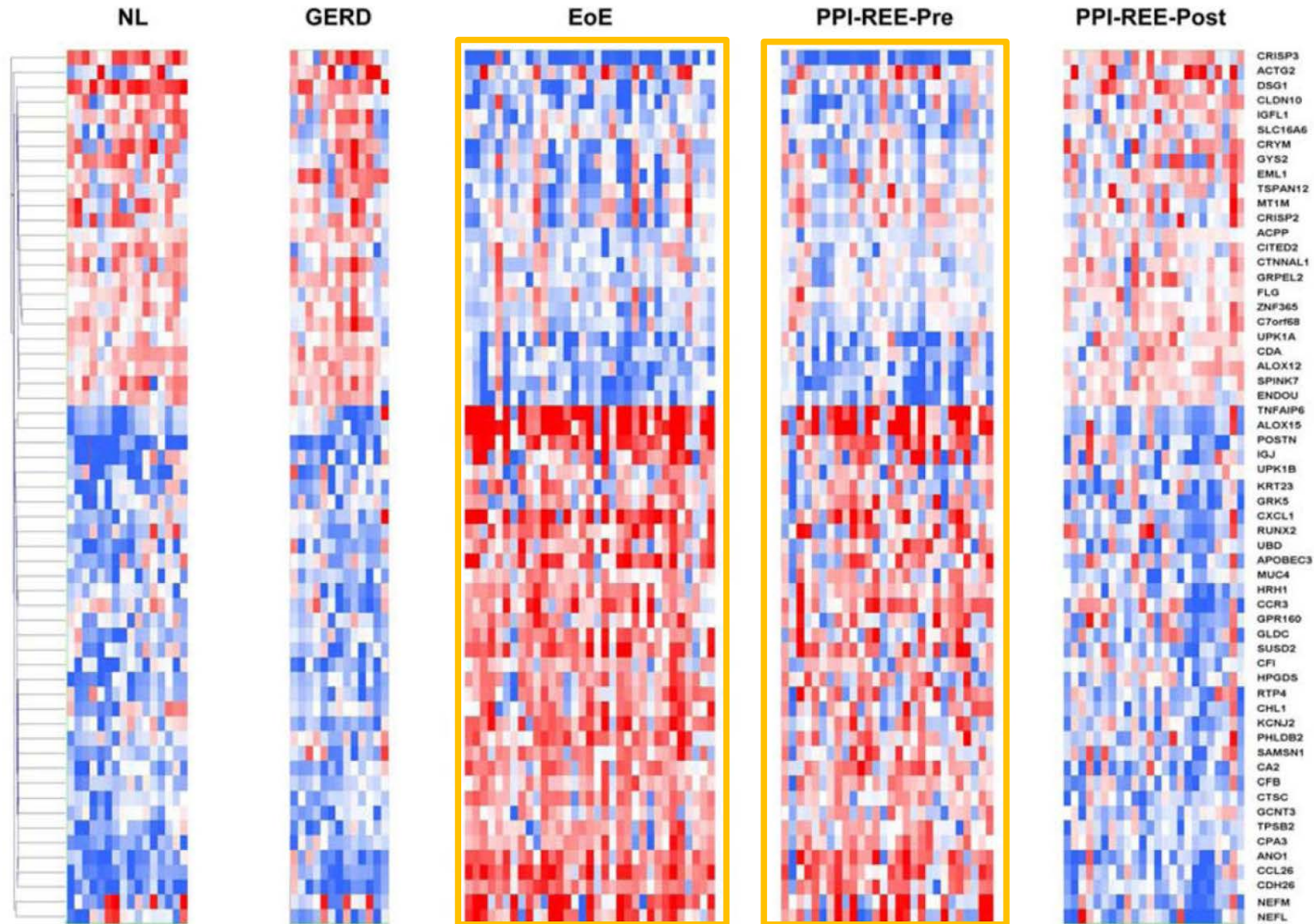




# 2015: Molecular profile of EoE and PPI-REE are similar



Wen et al JACI 2015





**12 month process involving 53 physicians  
(GI, allergy, pathology) (32 internists, 21 pediatricians)**

**4 teams reviewed world's literature**

Biologic impact of PPI

Evidence of PPI role in children and adults

Assessment of GERD

**8 hour Face to Face meeting- DDW 2017**





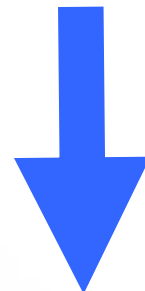
# New EoE Diagnostic Algorithm

Clinical presentation suggestive of **EoE**



EGD with biopsy

Esophageal eosinophilia > 15 eos/hpf (~60 eos/mm<sup>2</sup>)



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

**Eosinophilic E**sophagitis



# Conditions associated with esophageal eosinophilia



Eosinophilic esophagitis

Gastroesophageal reflux disease

Eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement

Achalasia and other disorders of esophageal dysmotility

Hypereosinophilic syndrome

Celiac Disease

Crohn's disease with esophageal involvement

Connective tissue disorders

Infections (fungal, viral)

Autoimmune disorders and vasculitides

Dermatologic conditions with esophageal involvement (ie pemphigus)


Drug hypersensitivity reactions

Pill esophagitis

Stasis esophagitis

Graft vs host disease

Mendelian disorders (Marfan Syndrome Type II, Hyper-IgE Syndrome, PTEN Hamartoma Tumor Syndrome, Netherton's Syndrome, Severe Atopy Metabolic Wasting Syndrome)







# EoE: Epidemiology

All ethnicities, all continents

Prevalence in US: ~ 1:2,000

Male:Female ~ 3:1

Familial Cases ~ 7%

Brother's relative risk ratio ~ 64-fold

Concordance

Monozygotic twins: 58%

Dizygotic twins: 36%

Non-twin siblings: 2.4%

Liacouras et al. J Allergy Clin Immunol. 2011;128(1):3-20  
Dellon ES, et al. Clin Gastroenterol Hepatol 2014;12:589-96  
Dellon ES, et al. Gastroenterology 2017

# Eosinophilic esophagitis: Updated consensus recommendations for children and adults

LIACOURAS ET AL

J ALLERGY CLIN IMMUNOL  
JULY 2011

## Co-morbid Allergic Disease Associated with EoE

### Pediatric Patients

42% to 93%

Allergic rhinitis  
40% to 75%

Asthma  
14% to 70%

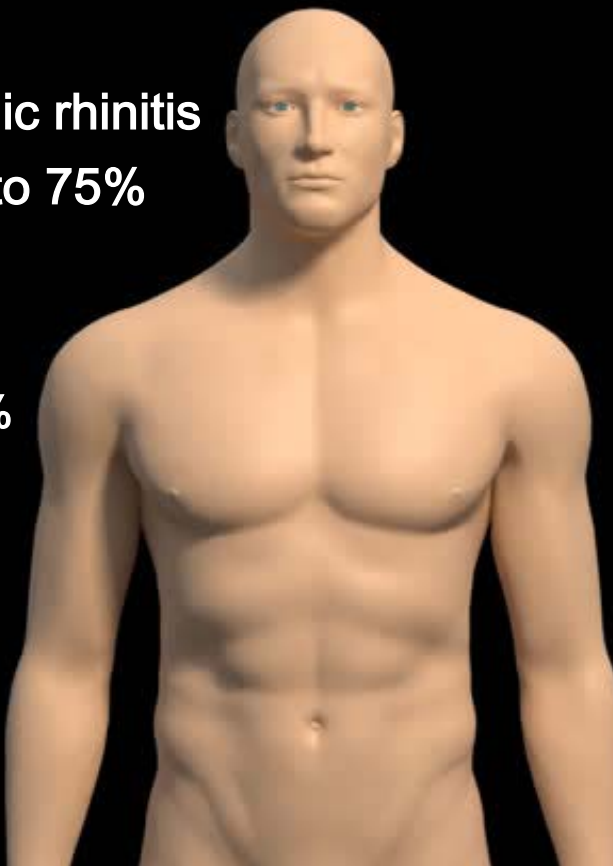
Atopic Dermatitis  
40% to 60%

### Adult Patients

28% to 86%

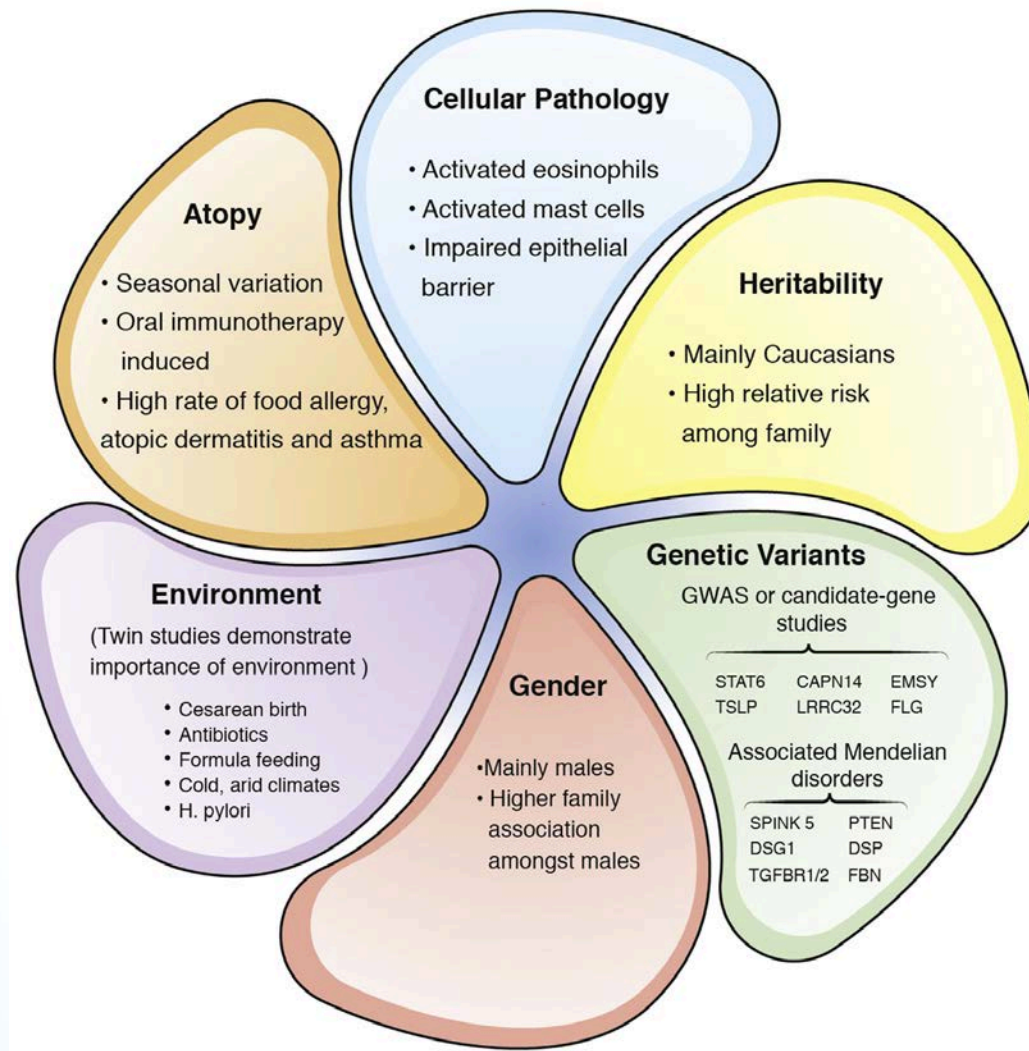
IgE-mediated food allergy  
15% to 43%

Elevated serum IgE level  
50% to 60%  
Peripheral eosinophilia  
40% to 50%






# EoE: Contributing factors

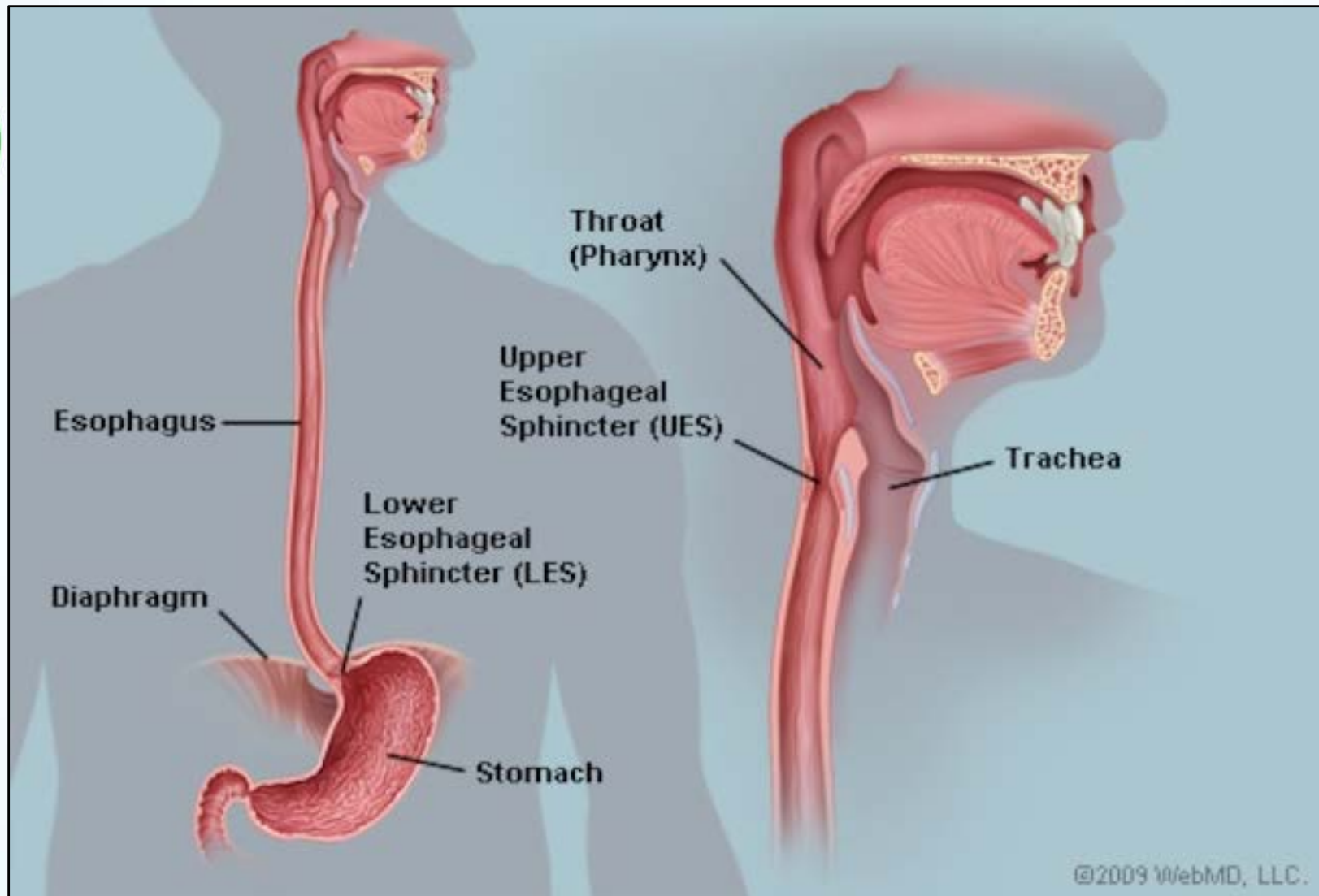






# EoE Triggers

- **Food Allergens**
  - **Airborne Allergens**
  - **Other allergens**
- 



The esophagus is a long, thin, and muscular tube that connects the pharynx (throat) to the stomach. It functions as the conduit for food and liquids that have been swallowed into the pharynx to reach the stomach.



# How much food does the average American eat over the course of a year?

The figure is a little hard to swallow: **1,996 pounds**, or nearly one ton. This is an estimate of how much — by weight — the average American eats over the course of one year.

The figure comes from economists who crunched food consumption data collected by the U.S. Department of Agriculture, Dec 31, 2011

[The Average American Ate \(Literally\) A Ton This Year: The Salt : NPR](#)

**20.4 gallons of milk**

**53 lbs of bread**

**547.5 Liters of saliva**

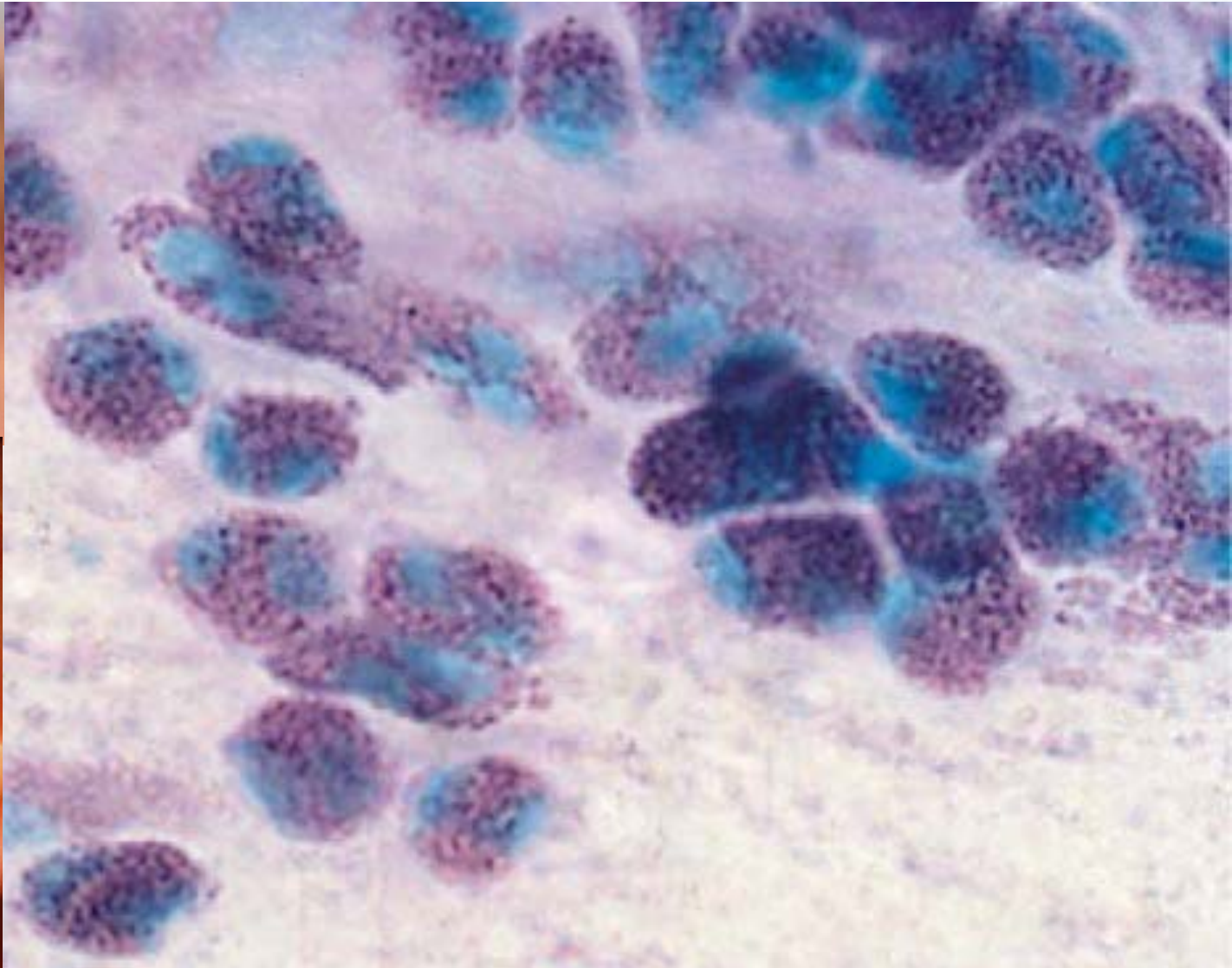




# Which Foods Trigger EoE?

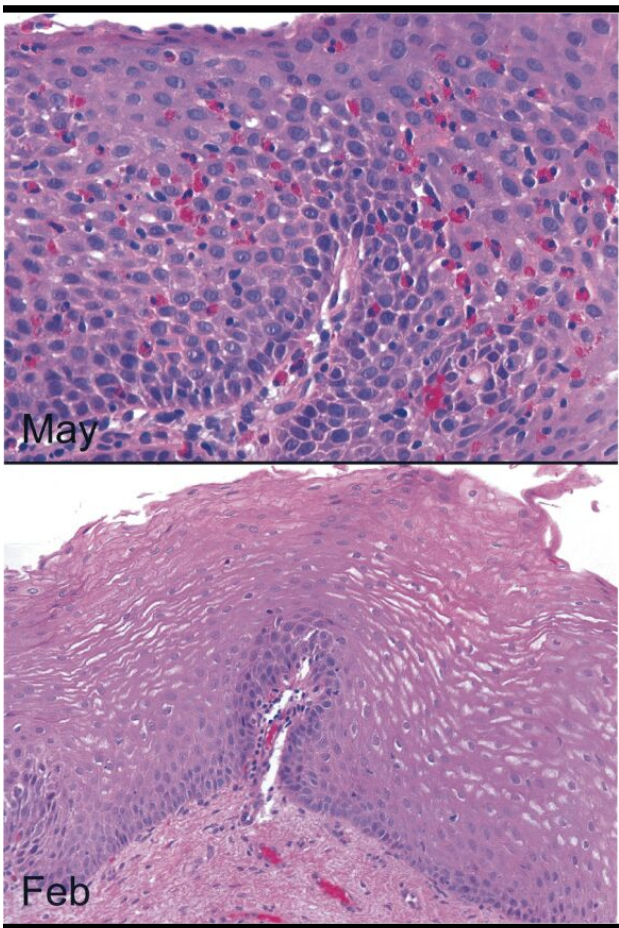
- **Most common food triggers worldwide**
  - Milk (about 2/3) > egg & wheat (another 1/4 patients)
- **Geographic and age differences**
  - US children: milk, egg & wheat
  - US adults: milk & wheat
  - Spain: soy & legumes are more common than in US
  - Peanut/tree nuts, fish/shellfish are less common
- **Number of foods driving disease**
  - 30 – 50%: one food
  - 30%: two foods
  - 30%: 3 or more food triggers

# Eosinophils in a nasal smear from a patient with allergic rhinitis

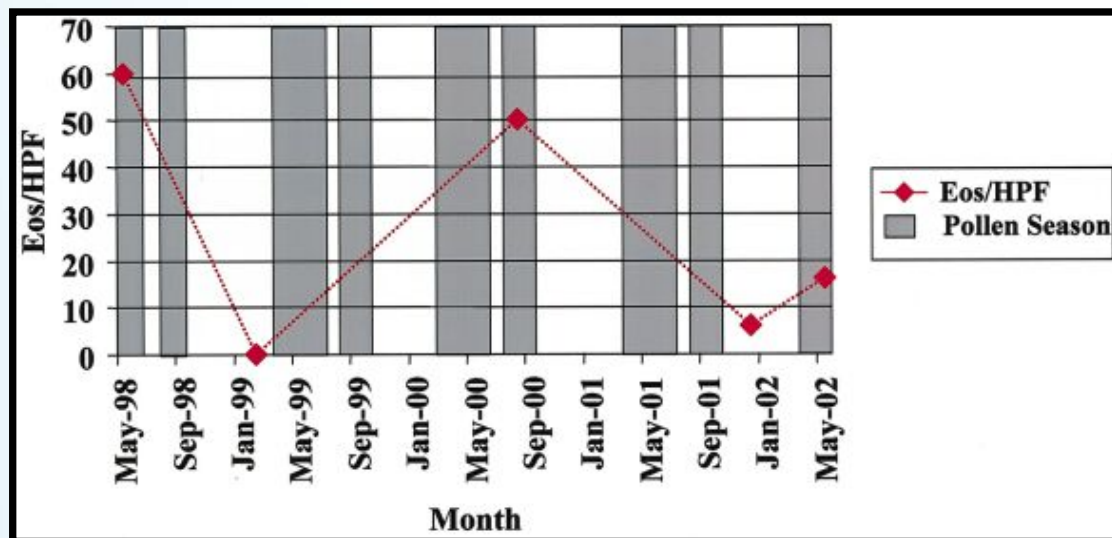




# Pollen and EoE



- 21 yo female with asthma and allergic rhinitis
- Dx May 1998 with EoE after presenting with reflux symptoms unresponsive to omeprazole
- Bx revealed normal duodenum and antrum with severe eosinophilic esophageal inflammation
- Repeat bx in Feb 99 during period of improvement was normal
- Spring 2000 seen by allergist with multiple positive skin tests to trees, grasses, ragweed, dog, cat, dust mite
  - Food skin tests and patch tests negative



- Environmental controls imposed
  - Worsened in spring and summer of 2000
  - August 2000, repeat bx, eos infiltration
  - Dec 2001, repeat bx, 6 eos/hpf
  - Temporal association between pollen exposure and worsening
- Spergel JM, et al. JACI 112:796, 2003

# Pollen-Food Allergy Syndrome (Oral Allergy Syndrome)

## Patients

- Occurs in some pollen allergic patients

## Mechanism

- Primary sensitization to pollen with subsequent reaction to cross-reacting allergens in fruits and vegetables

## Symptoms

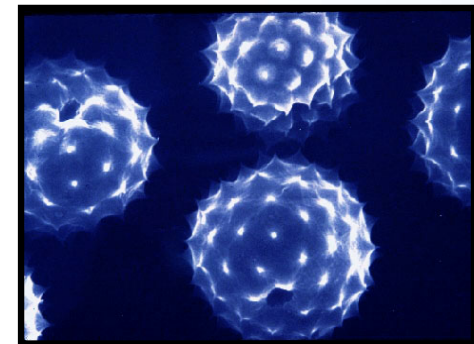
- Symptom onset during or soon after food ingestion
- Pruritus & edema of lips, tongue and palate
- Systemic symptoms can occur

## Laboratory

- Prick to prick skin tests or skin tests with fresh extracts of implicated foods are positive

## Treatment

- Avoidance with severe symptoms
- Patients usually tolerate same fruit or vegetable when cooked



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# Association of eosinophilic esophagitis and food pollen allergy syndrome

*Letters / Ann Allergy Asthma Immunol 118 (2017) 108–122*



**Table 1**

Demographic and Clinical Characteristics of 186 Patients With Eosinophilic Esophagitis and 209 Patients With Allergic Rhinitis Visited at Northwestern Medicine or Rush University Medical Center Between 2005 and 2014<sup>a</sup>

Variable	Patients with eosinophilic esophagitis (n = 186)	Patients with allergic rhinitis (n = 209)	P value
Male	104 (55.3)	109 (52.1)	.93 ( $\chi^2$ test)
Age, mean (SD), y	38.08 (11.9)	37.65 (14.5)	.74 (t test)
Asthma	57 (30.3)	62 (29.7)	.46 ( $\chi^2$ test)
Symptomatic allergic rhinitis	106 (56.4)	209 (100)	<.001 ( $\chi^2$ test)
Sensitization to at least 1 aeroallergen	168 (90.4)	209 (100)	<.001 ( $\chi^2$ test)
Sensitization to at least 1 pollen (tree, grass, and/or weed)	155 (82.4)	146 (69.9)	<.001 ( $\chi^2$ test)
Symptomatic PFAS among all cases	79 (42)	15 (7.2)	<.001 ( $\chi^2$ test)
Symptomatic PFAS among pollen-sensitized cases	79/155 (50.9)	15/146 (10.2)	<.001 ( $\chi^2$ test)

Abbreviation: PFAS, pollen food allergy syndrome.

<sup>a</sup>Data are presented as number (percentage) of patients unless otherwise indicated.

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# Symptoms Suggestive of EoE

Infant



Adult

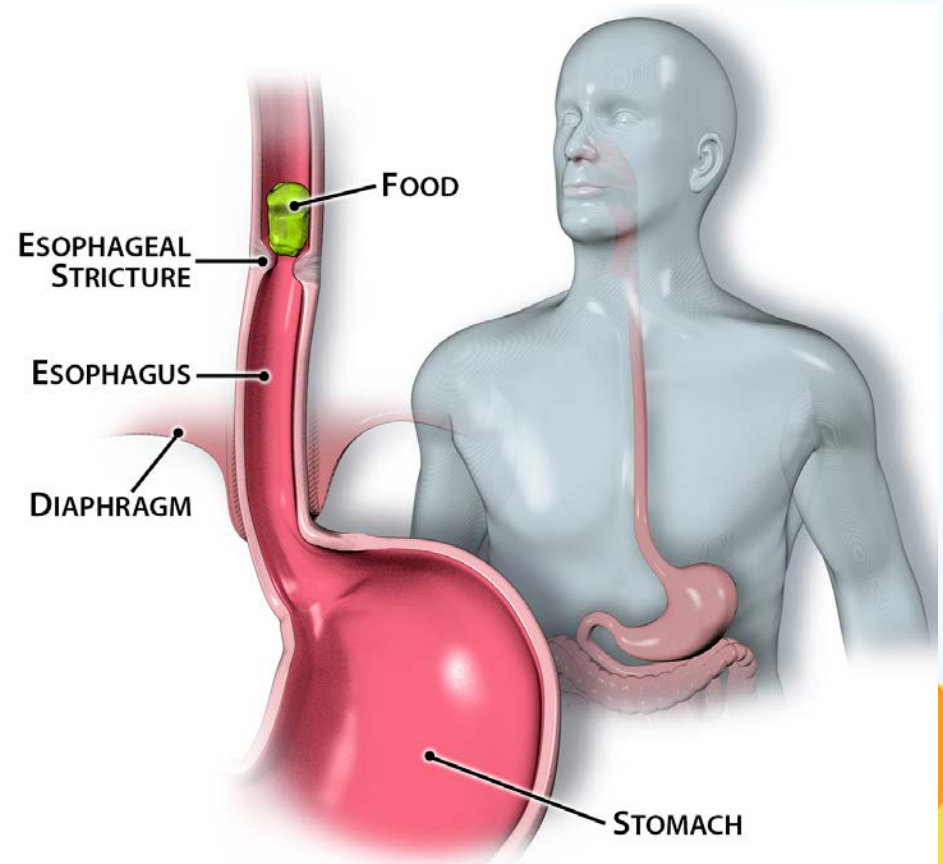
- Feeding aversion or intolerance
- Failure to thrive
- Vomiting
- Epigastric or chest pain
- Dysphagia
- Food impaction





# Food Impaction is a common presenting symptom of EoE

- Prospective study
- 33 adults seen in ER with food impaction over 3 years(2002-05)
- 17 (51%) with EoE



Desai T et al Gastrointest Endosc 2005

Hurtado-Waasdorp C et al J Pediatr Gastroenterol Nutr 2010

# EoE History: Questions



Are you a slow eater? Picky eater?

Do you have trouble swallowing foods?

Do foods get stuck in your throat?

Do you always take small bites?

Do you always chew your food a lot?

Do you put sauces on all your foods?

Do you need to drink lots of liquids with your meals?

Do you avoid highly textured or dense foods?

Do you hold foods in your mouth rather than swallow them?  
(chipmunking)

Do you cough and choke during meals?

Do you have to leave the table to  
get foods out of your esophagus?

Do you avoid eating in public?





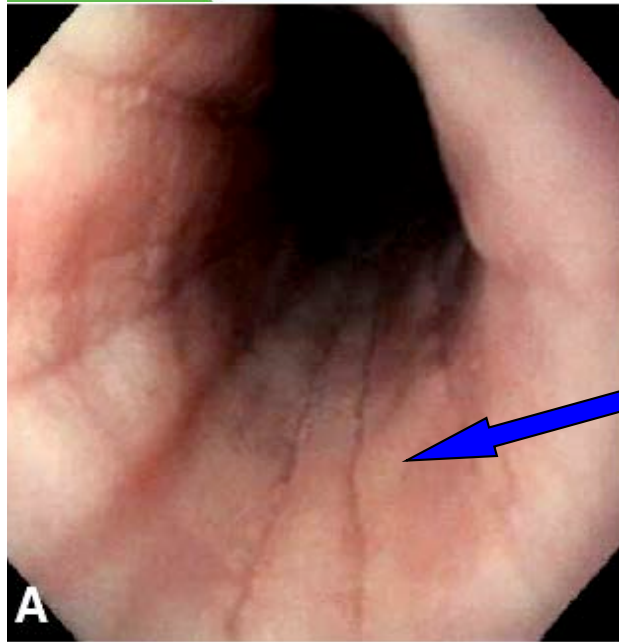


# Other Findings in the History Associated with EoE

- Family history of severe GERD, strictures, dysphagia, dilations, EoE
- “GERD refractory to medical and/or surgical management”
- Family history of allergic disease
- Personal history of allergic disease



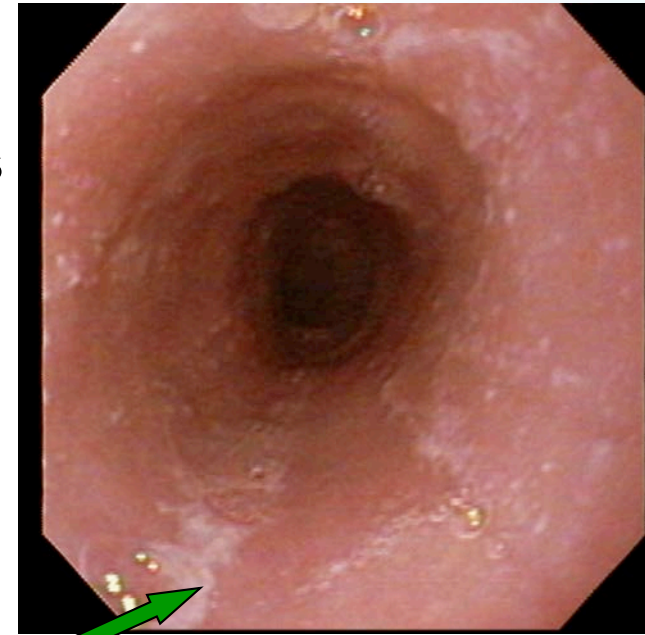
# Endoscopic Findings in EoE



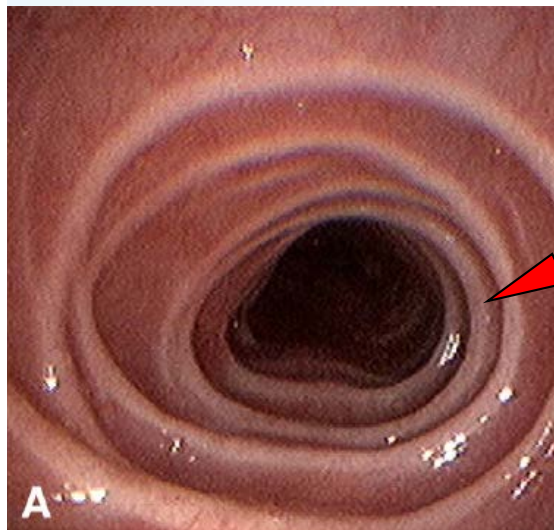
Linear furrowing, vertical lines  
of the esophageal mucosa

**Furrows**

White exudates, white  
specks, nodules, granularity



**Exudates**

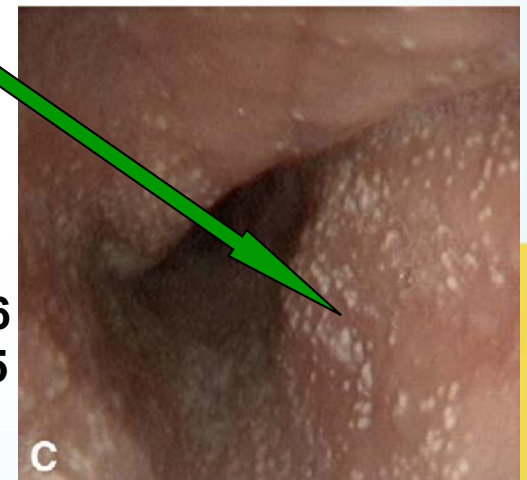


Circular rings,  
transient or fixed

**Rings**

Fox V et al. *Gastrointest Endo* 2003;57:30-36  
Desai T et al. *Gastrointest Endo* 2005;61:795  
Straumann A et al. *Gastrointest Endo* 2003;  
57:407

Gonsalves N, et al. *Gastrointest Endosc*  
2006;64:313-9

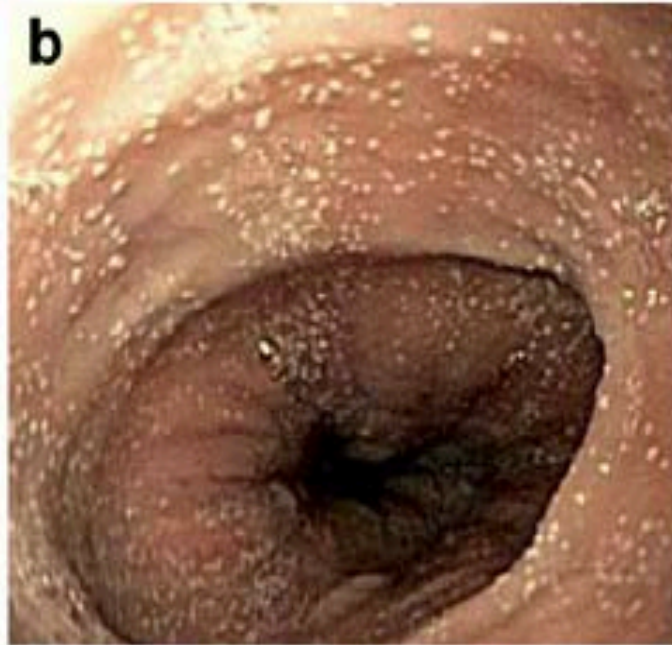




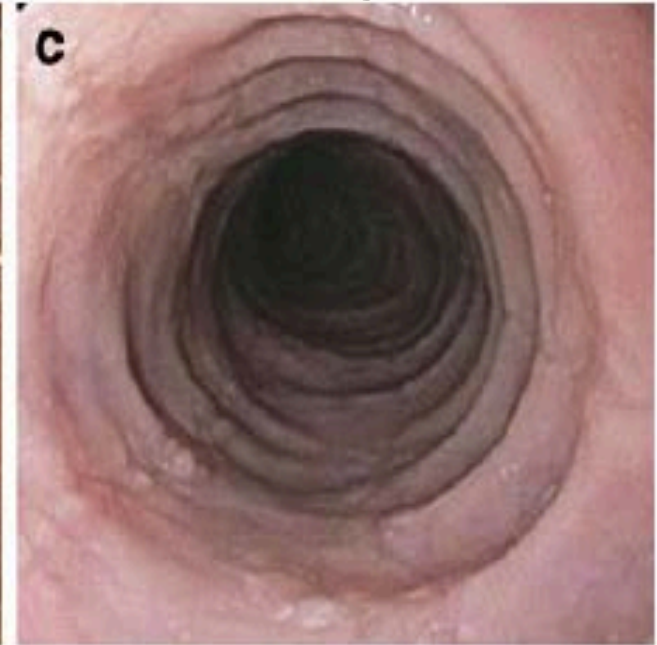
**Normal**



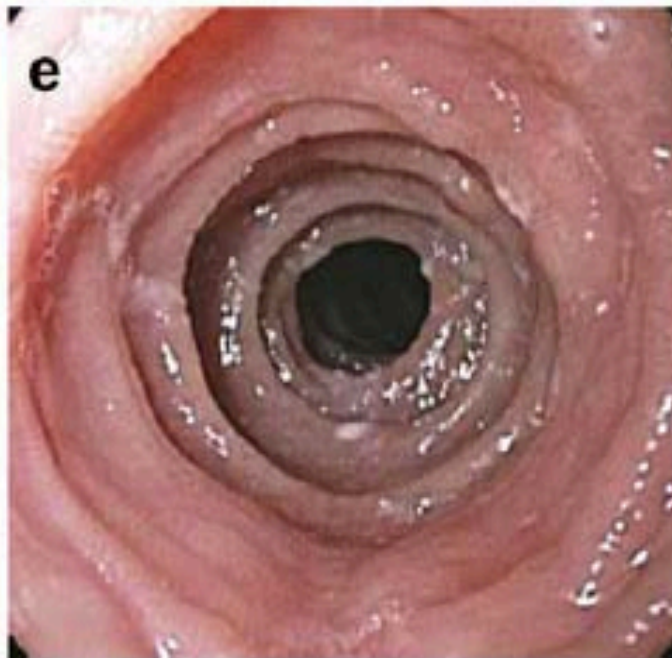
**White Exudate**



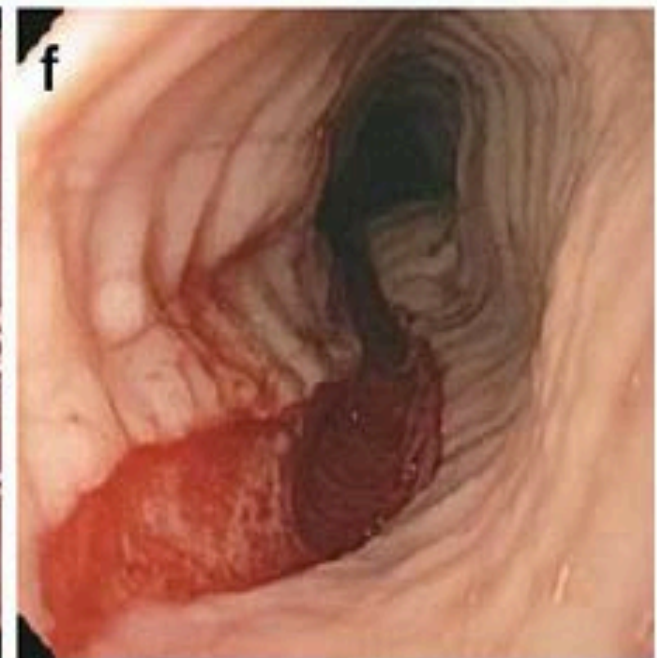
**Rings**



**Furrows**

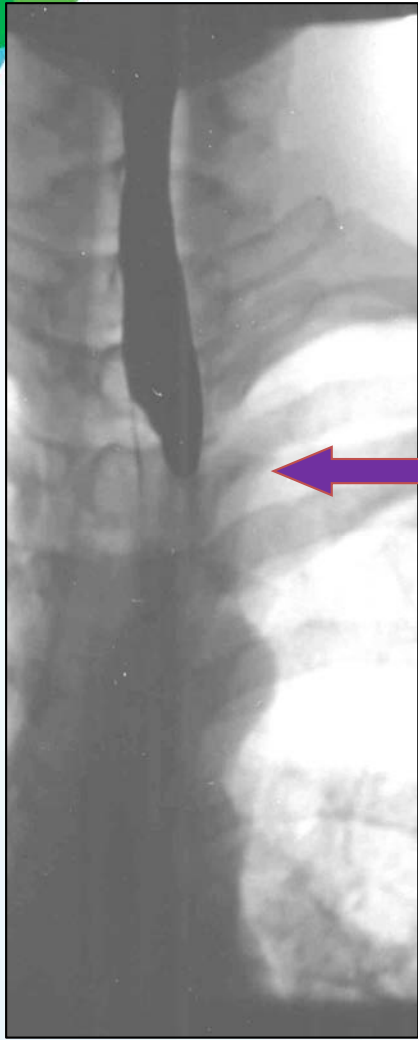


**Strictures**

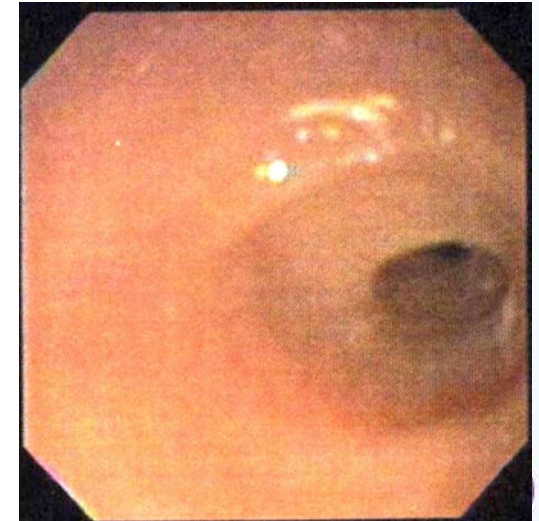


**Longitudinal tear**

# Endoscopic Findings in EoE



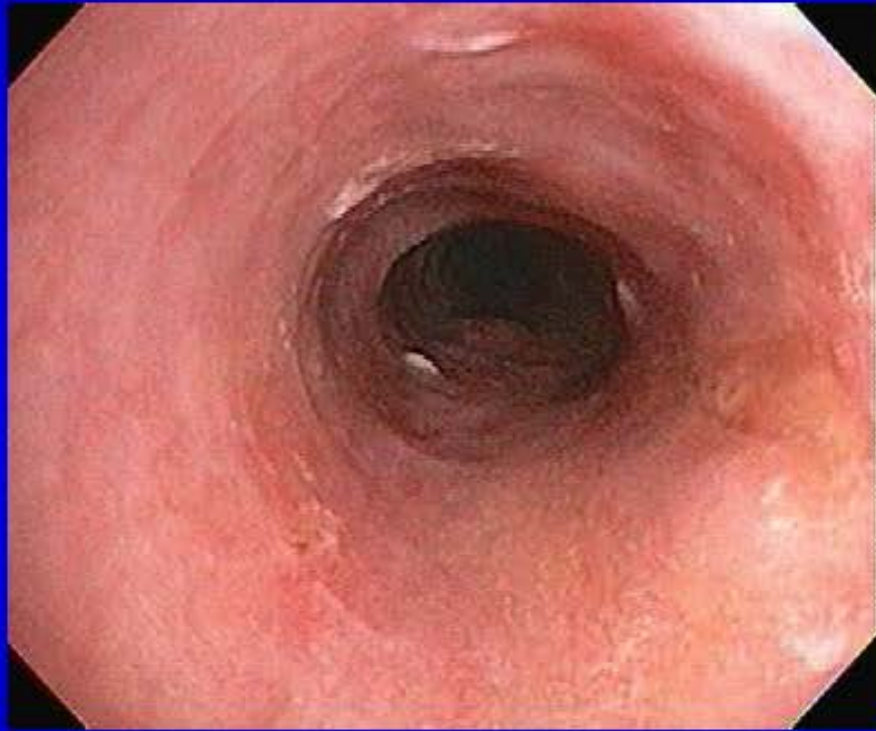
Esophageal stricture:  
proximal, middle or distal



32 year old woman with life-long history of dysphagia, who took hours to eat and was previously diagnosed with GERD and hysteria

Courtesy of S. Rosenberg, MD, T Lembo, MD





**Long segment esophageal narrowing**



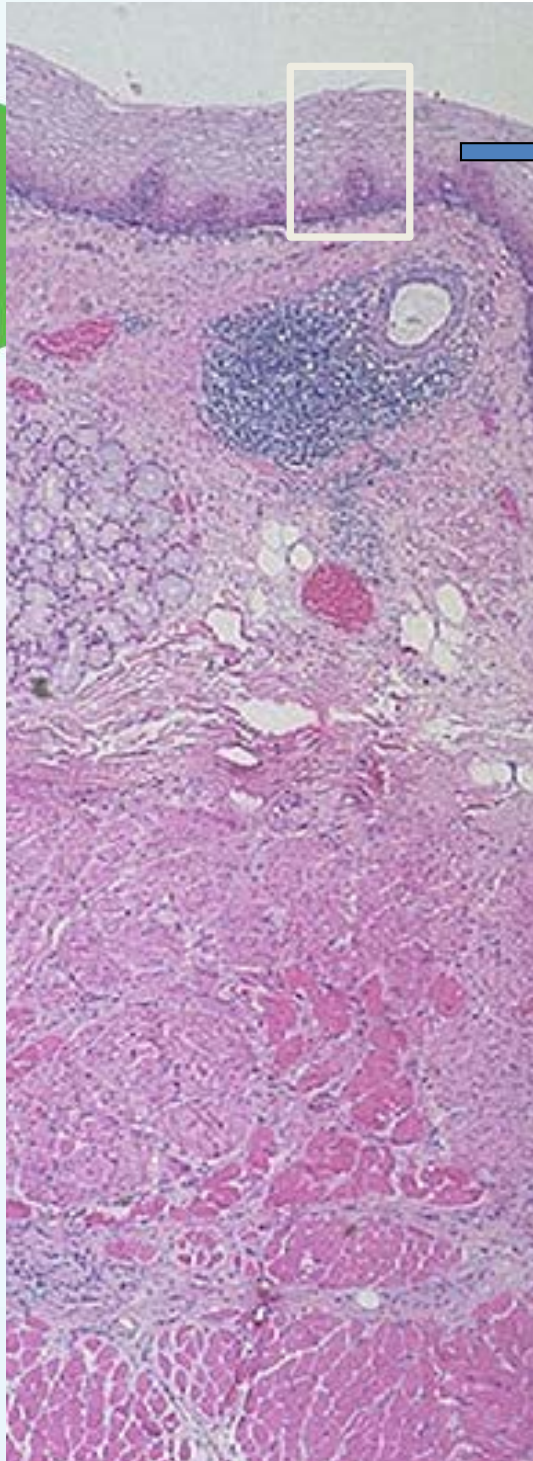




# Diagnostic clues/cautions

- At risk: SLIT, OIT, outgrew IgE-mediated food allergy with food in diet
- “Pretreated mucosa”-i.e. use of topical steroids for other atopic diseases may diminish esophageal inflammation
- Prior normal endoscopy doesn’t rule out EoE.
- Normal appearing endoscopy still requires biopsies.
- Abnormal endoscopy/histology is not diagnostic of EoE.





**Small sample size**

***Mucosal biopsy samples (3 mm) = 0.01%  
of surface area***

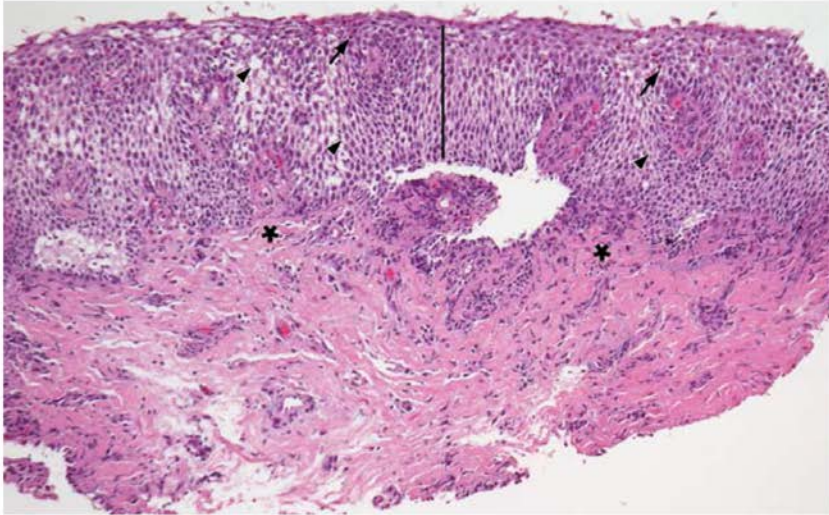
# Histologic Features of EoE



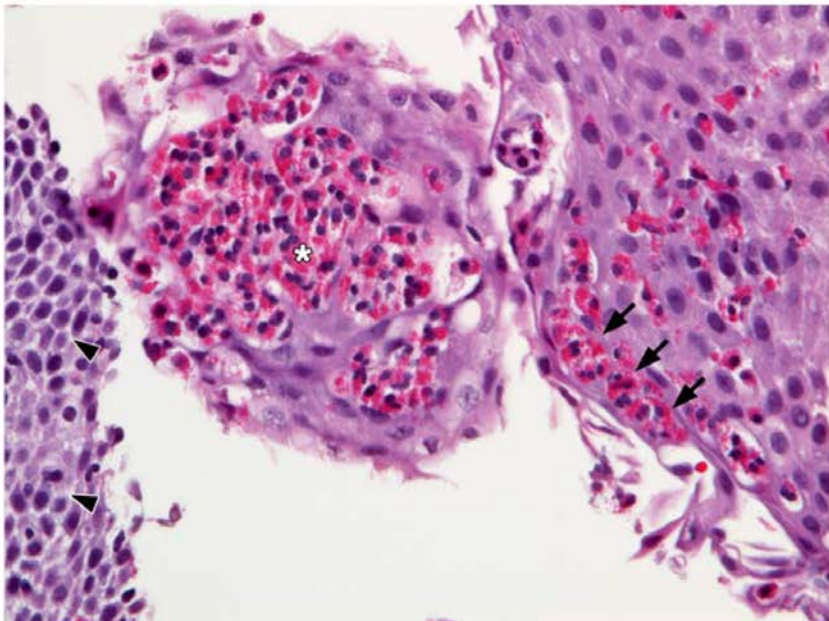
## More than eosinophilia

- Eosinophil number
- *Basal zone hyperplasia*
- *Dilated intercellular spaces*
- *Eosinophil abscesses*
- *Superficial layering of eosinophils*

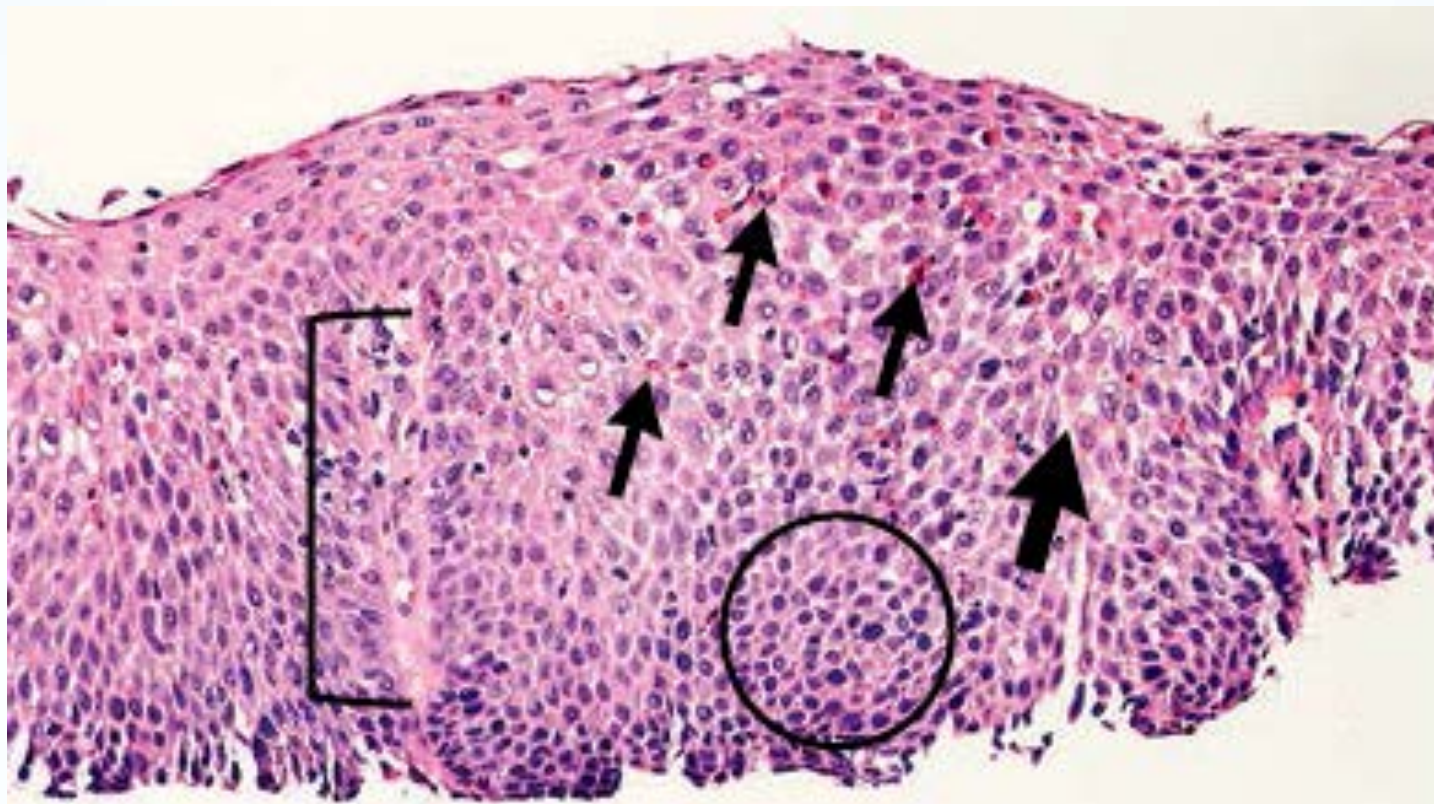
(a)



(b)



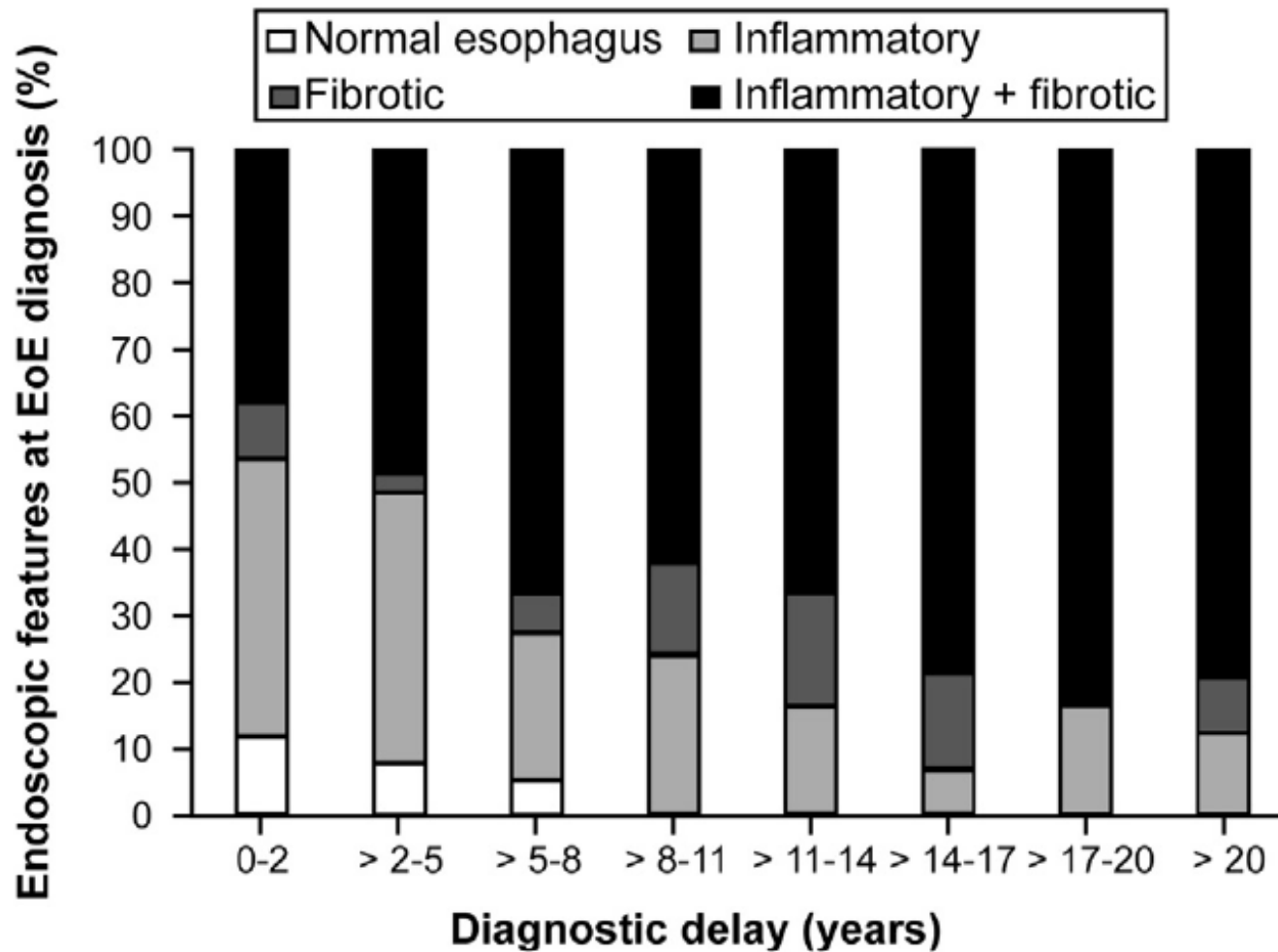




**Figure 2. Histologic Characteristics of Eosinophilic Esophagitis.**

Routine staining with hematoxylin and eosin reveals numerous eosinophils (thin arrows), dilated intercellular spaces (thick arrow), basal zone hyperplasia (circle), and papillary elongation (bracket).

# Untreated EoE leads to fibrosis





# EoE Complications

- Feeding dysfunction / malnutrition / failure to thrive
- Esophageal stricture
- Esophageal food/foreign body impaction
- Cancer is NOT a complication of EoE





## **Clinical tolerance in eosinophilic esophagitis** JACI IP 2018;6:663

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Amanda B. Muir, MD<sup>b</sup>, Chris A. Liacouras, MD<sup>b</sup>, and

Jonathan M. Spergel, MD, PhD<sup>a</sup>

## **Natural History of EoE**

### *Clinical Implications*

- Although food allergens play a pathologic role in eosinophilic esophagitis (EoE), the role of clinical tolerance in EoE remission is less clear. In this study, we conducted retrospective review of pediatric EoE population and identified patients managed with dietary therapy who achieved histologic remission on reintroduction of open diet, consistent with periods of prolonged clinical tolerance.
- 

# Clinical Tolerance in EoE



Ruffner MA, et al. JACI IP 2018;6:663

## Database of 1,812 patients

No.	Sex	Age at diagnosis (y)	Race	Comorbid conditions	Presenting symptoms	Initial biopsy (eos/hpf)	Management	Duration on elimination diet (y)	% time biopsy clear while on elimination diet	No. of clear follow-up endoscopy with biopsies after open diet	Follow-up interval after open diet (y)
1	F	8	White	AR	Dysphagia, impaction	40	Elimination diet	9.1	43.5	3	4.3
2	M	4	White	Asthma, AR	Regurgitation, vomiting	60	Elemental formula, then diet reintroduction	10.1	51.2	3	1
3	F	1.5	White	Asthma, AR	Regurgitation, vomiting	25	Elimination diet	2.9	82.6	4	9.7
4	M	6	White	AR	Dysphagia	30	Elimination diet	3.4	20.7	2	2.7
5	M	11	White	AR, ADHD	Dysphagia	45	Elimination diet	1.7	58.8	1	6.4
6	F	10	White	AR, OAS	Abdominal pain, vomiting	50	Elimination diet + environmental allergen immunotherapy	4.5	70.4	2	2.5
7	M	3	White	Asthma, AR	Regurgitation, reflux	20	Elimination diet + 1-mo swallowed steroids	10.1	58.3	2	0.5
8	M	5	White	Asthma, AR	Food aversion, slow eating	25	Elimination diet + swallowed steroids	4.8	82.0	1	0.75
9	F	7	Asian	IgE-FA, AD, asthma	Dysphagia	30	Elimination diet	2.1	17.9	4	1.6

AD, Atopic dermatitis; ADHD, attention deficit/hyperactivity disorder; AR, allergic rhinitis; eos, eosinophils; F, female; IgE-FA, IgE-mediated food allergy; M, male; OAS, oral allergy syndrome.





# Algorithm for the Diagnosis and Management of Eosinophilic Esophagitis

## Symptoms

- Difficulty feeding
- Vomiting
- Failure to thrive
- Epigastric or chest pain
- Dysphagia
- Food impaction

**Esophagram?**

**Endoscopy with biopsies**

**Esophageal Eosinophilia  
 $\geq 15$  eos/hpf ( $\sim 60/\text{mm}^2$ )**

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

## Other findings increasing the likelihood of EoE

- Family hx of allergic disease
- Family hx of severe GERD, strictures, dysphagia, or EoE
- Personal hx of allergic disease

**Findings inconsistent with EoE**

**Treat for GERD or other dx & monitor clinical course**

# Algorithm for the Diagnosis and Management of Eosinophilic Esophagitis



## Symptoms

- Difficulty feeding
- Vomiting
- Failure to thrive
- Epigastric or chest pain
- Dysphagia
- Food impaction

Esophagram?

Endoscopy with biopsies

Esophageal Eosinophilia  
 $\geq 15$  eos/hpf ( $\sim 60/\text{mm}^2$ )

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

Findings consistent  
with EoE

Treatment options

3Ds

- Diet
- Drugs
- Dilation

## Other findings increasing the likelihood of EoE

- Personal hx of allergic disease
- Family hx of allergic disease
- Family hx of severe GERD, strictures, dysphagia, or EoE



# Eosinophilic Esophagitis: Treatment

## Diets

Elemental diet

6-, 4-, 2-, 1-food empiric elimination diets

Tailored, targeted diet

## Drugs

PPI

Swallowed topical steroids

## Dilation



# What about 'allergy tests' for EoE?



- Skin tests and serum IgE tests are effective for the diagnosis of IgE-mediated allergy
- EoE is not an IgE-mediated disease
- Skin tests and serum IgE tests are not reliable tests for identifying foods causing EoE



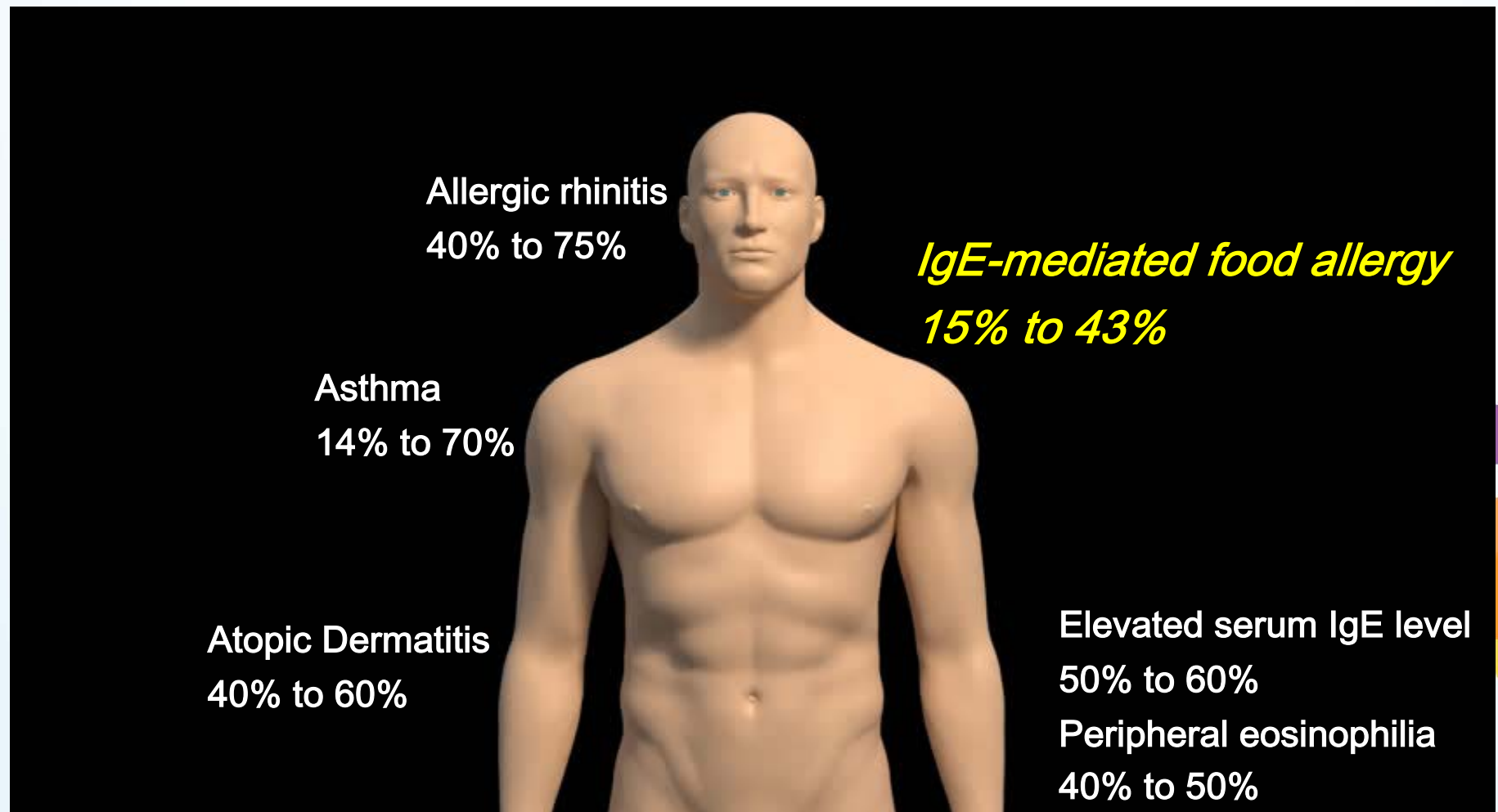


# Eosinophilic esophagitis: Updated consensus recommendations for children and adults

LIACOURAS ET AL

J ALLERGY CLIN IMMUNOL  
JULY 2011

## Co-morbid Allergic Disease Associated with EoE

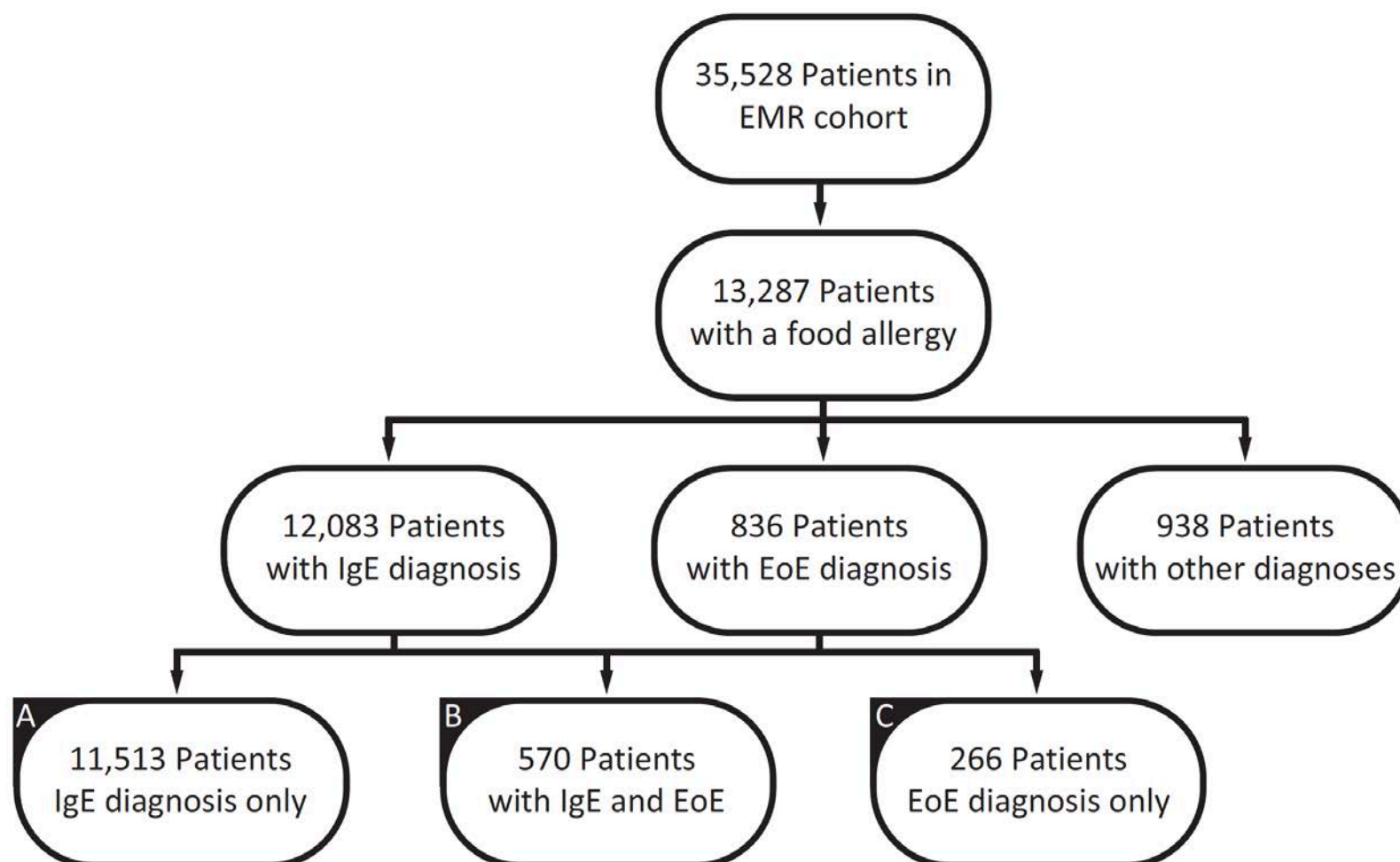


# The Prevalence of Eosinophilic Esophagitis in Pediatric Patients with IgE-Mediated Food Allergy



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	Rate	Source	References
General population	0.0004	ICD, Survey	29, 30
IgE population	0.0472	ICD	

ICD, International Classification of Diseases.

# The Occasional Ebb and Flow between Eosinophilic Esophagitis and IgE-Mediated Food Allergy

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## Food allergy → EoE

- Oral immunotherapy to milk, egg, peanut: ~3%
- Food allergic patients who outgrow their food allergy and add the food to their diet
  - 17/84 developed EoE with average time to diagnosis of 2.4 years after food introduction

## EoE → Food allergy

- ~2% of patients placed on an empiric diet eliminating cow's milk could develop milk allergy



# Role for 'allergy tests' in EoE?



## Foods

- IgE-mediated food allergy is suspected
- Empiric elimination diets did not work
- Before removal of common food allergen from diet
- Prior to reintroduction of common food allergen to diet

## Environmental allergens

- Allergic rhinitis is suspected
- Presence of other allergic disease – asthma, eczema, animal allergy





# Proton Pump Inhibitors (PPIs)

PPIs should be considered first line therapy for suspected EoE with treatment lasting at least 8 weeks

Dosing: 20-40 mg of selected PPI twice daily

36-71% have remission of esophageal eosinophils with PPI therapy alone - previously referred to as PPI-responsive EoE (PPI-REE)<sup>1</sup>

There are no baseline clinical, molecular, endoscopic, or histological features that distinguish PPI-REE from EoE, which led to retirement of this terminology.<sup>2</sup>

## Potential benefits with long-term use

- Symptom improvement
- Anti-inflammatory properties of PPIs
- Promotes healing of esophageal mucosal tissue
- Reversal of gene expression associated with allergic inflammation

<sup>1</sup>Vazquez-Elizondo G, et al. Aliment Pharmacol Ther 2013; 38: 1312-9

<sup>2</sup>Gutierrez-Junquera C, et al. J Pediatr Gastroenterol Nutr 2016; 62: 704-10



# Topical Steroid Treatments for EoE



Fluticasone (Flovent): 2 puffs twice a day

1–5 yr, 44  $\mu$ g

11 yr, 110  $\mu$ g

12 yr and older, 220  $\mu$ g

Budesonide (Pulmicort): Respules mixed with Splenda twice a day

1–5 yr, 0.25 mg/2 ml

6–11 yr, 0.5 mg/2 ml

12 yr and older, 1 mg/2 ml

Regularly review technique with patient. No rinsing of mouth, eating or drinking for 30 minutes after topical steroid administration







# Esophageal Dilation

Does not affect the underlying disease process

Risk of rupture: 0.3%

Best utilized in the presence of esophageal stricture, significant dysphagia, or lack of response to other therapies

Nearly half of patients will remain symptom free 1 year after dilation

40% will remain symptom free 2 years after dilation

Not recommended as monotherapy

