EGID Pathogenesis

Seema S. Aceves, MD, PhD
Associate Professor, Pediatrics and Medicine
Director, Eosinophilic Disorders Clinic
University of California, San Diego
Rady Children's Hospital, San Diego

EoE:
A Clinicopathological Diagnosis

Differential Diagnosis of Esophageal Eosinophils

- Gastroesophageal Reflux Disease
- Eosinophilic esophagitis
- Eosinophilic gastroenteritis with esophageal involvement
- Hypereosinophilic syndrome
- Parasitic infection
- Drug allergy
- Connective tissue disorder (scleroderma)
- ?Celiac with esophageal eosinophilia

2011 Consensus Recommendations

Eosinophilic esophagitis: Updated consensus recommendations for children and adults

Chris A. Liacouras, MD, Glenn T. Furuta, MD, Ikuo Hirano, MD, Dan Atkins, MD, Stephen E. Attwood, MD, FRCS, FRCSI, MCh, Peter A. Bonis, MD, A. Wesley Burks, MD, Mirna Chehade, MD, Margaret H. Collins, MD, Evan S. Dellon, MD, MPH,

Conceptual definition

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

Liacouras et al, 2011 Updated Consensus Recommendations, JACI

Eosinophilic esophagitis: Updated consensus recommendations for children and adults

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Diagnostic guideline

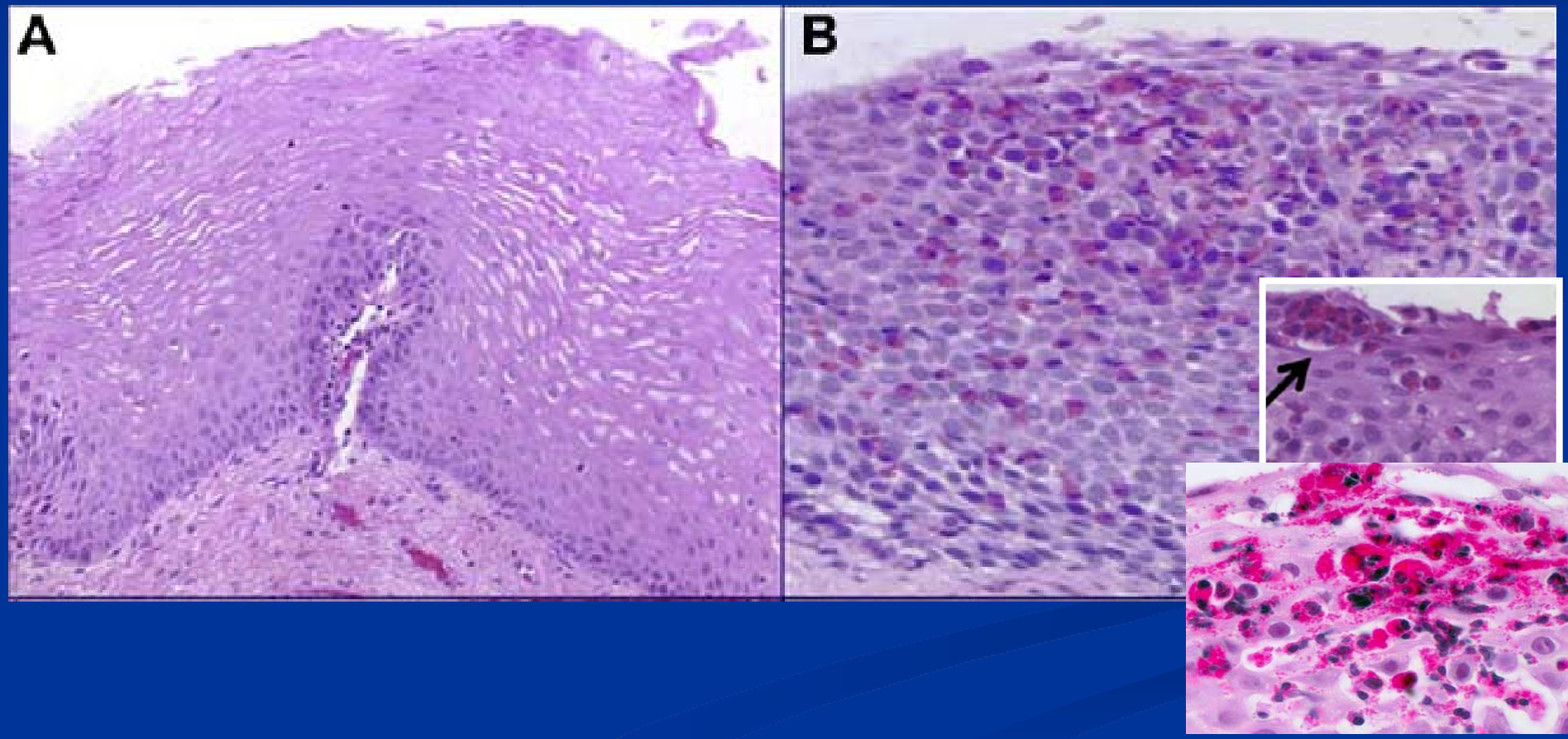
EoE is a clinicopathologic disease. Clinically, EoE is characterized by symptoms related to esophageal dysfunction. Pathologically, 1 or more biopsy specimens must show eosinophil-predominant inflammation. With few exceptions, 15 eosinophils/hpf (peak value) is considered a minimum threshold for a diagnosis of EoE. The disease is isolated to the esophagus, and other causes of esophageal eosinophilia should be excluded,

Liacouras et al, 2011 Updated Consensus Recommendations, JACI

Histologic Features

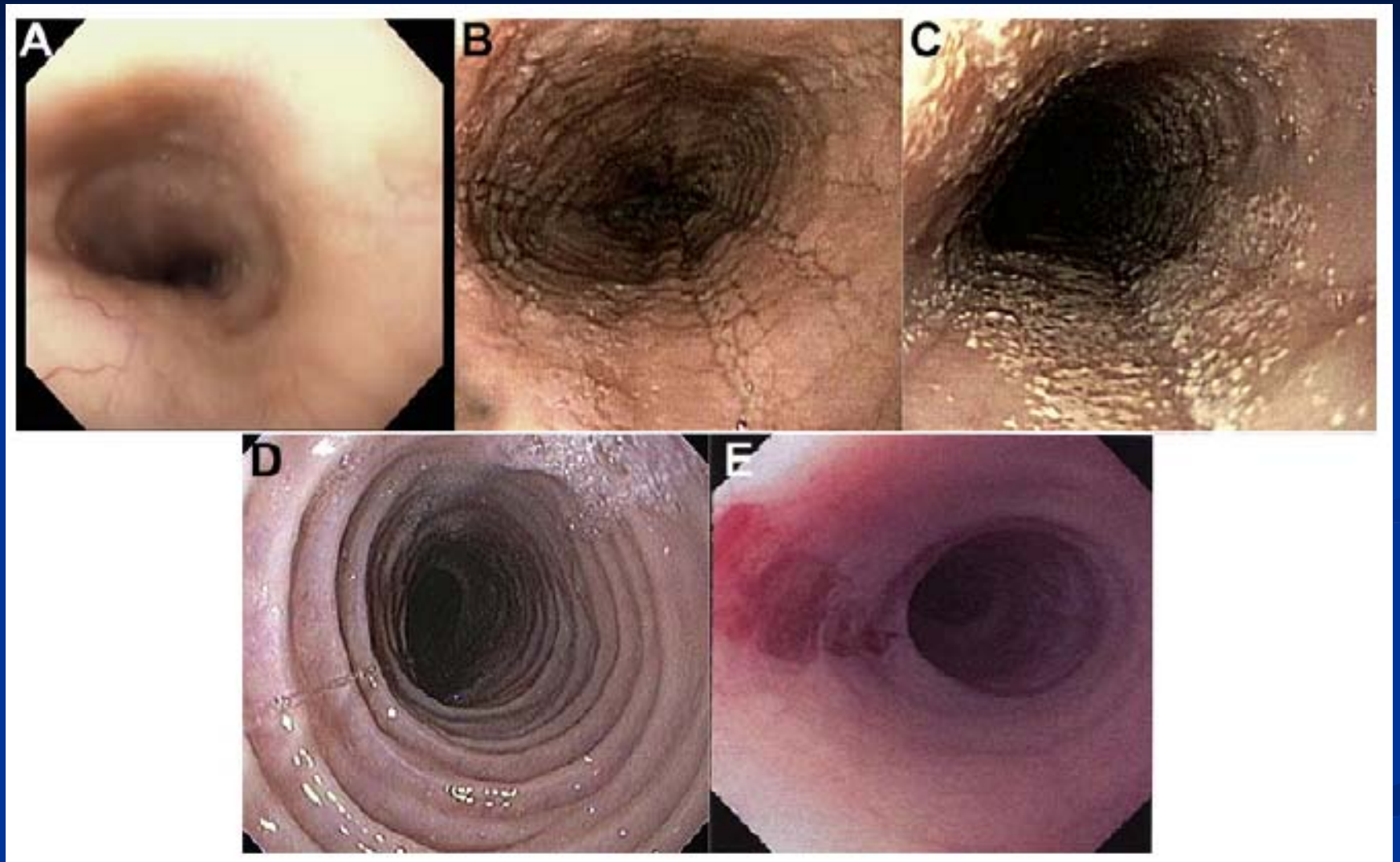
>15 eosinophils per hpf
Eosinophil Degranulation
Basal Zone Hyperplasia
Dilated Intercellular Spaces

Histologic Features



Liacouras et al, 2011 Updated Consensus Recommendations, JACI

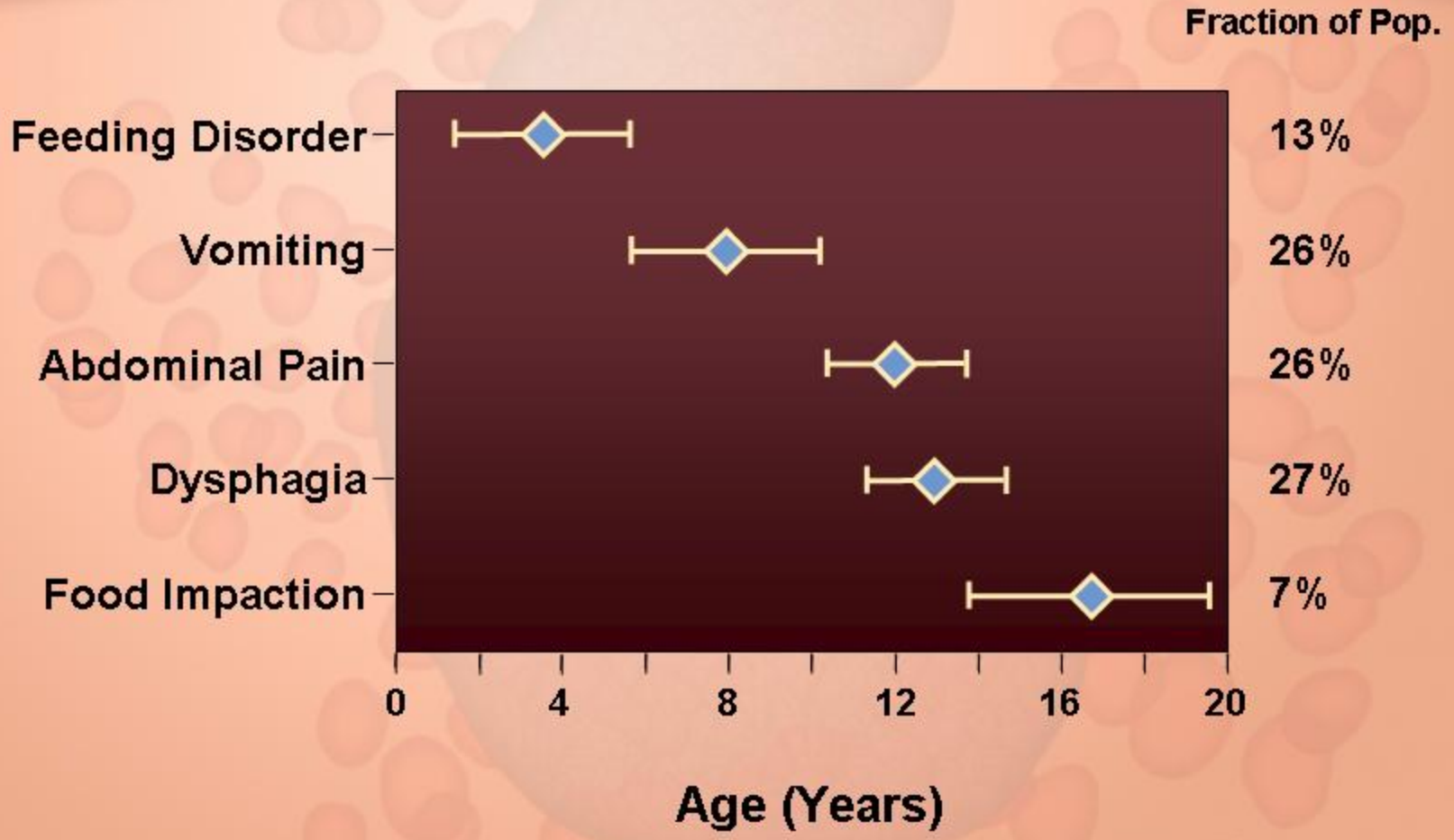
Endoscopic Features



Liacouras et al JACI, 2011

Symptoms and Clinical Features

EoE Presentation by Age



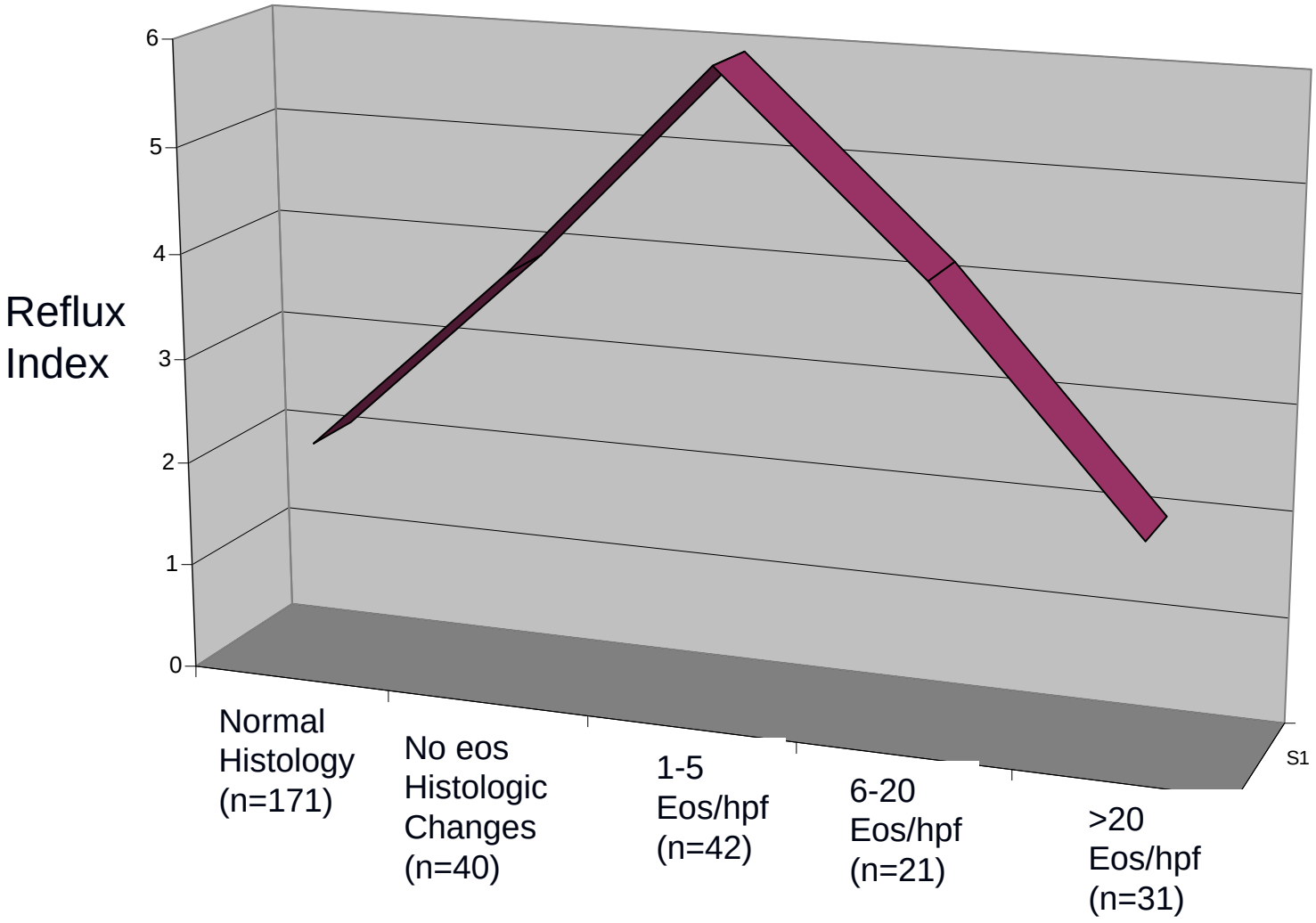
Noel, et al; *N Engl J Med* 2004; 351:940.

Pathogenesis: Triggers for Eosinophilia

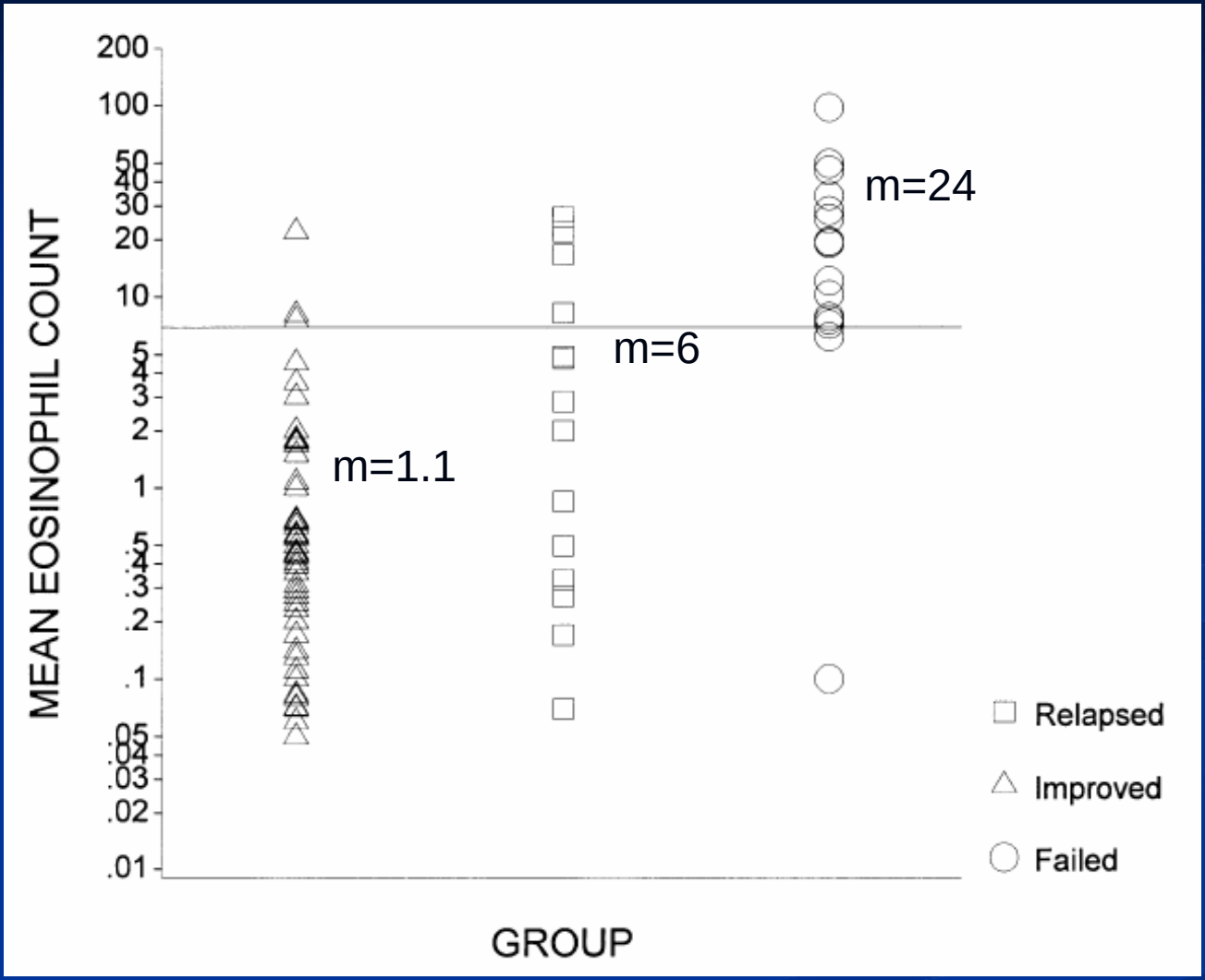
- Acid
- Aeroallergens

Acid Driven Eosinophilia

Reflux Index To Eosinophilia



Steiner et al, Am J Gastroenterol, 2004



Ruchelli et al, Ped Dev Path, 1998

Eosinophils and GERD

	Patient 1	Patient 2	Patient 3
Age (yr)/sex	14/M	25/M	13/F
Presentation	Pain	Food impaction	Dysphagia
Environmental Allergies	Yes	Yes	No
Treatment	Omeprazole 10 mg BID	Omeprazole 20 mg BID	Omeprazole 20 mg QD
Eosinophils/hpf			
Before treatment	37	21	59
After treatment	1	3	0

Ngo, et al; *Am J Gastroenterol* 2006;101:1666.

PPI Responsive Esophageal Eosinophilia

- Adult patients

An emerging body of literature and clinical experience describes a subset of patients whose symptoms and histopathologic findings are responsive to PPI treatment and who might or might not have well-documented GERD. Until more is known regarding this subgroup of patients, these patients should be given diagnoses of PPI-responsive esophageal eosinophilia. Future studies should be performed to determine whether PPIs help to diminish an immune/antigen-driven response, as is known to occur in patients with EoE.

  - Eosinophils >15 per hpf
  - 40% Responded to PPI

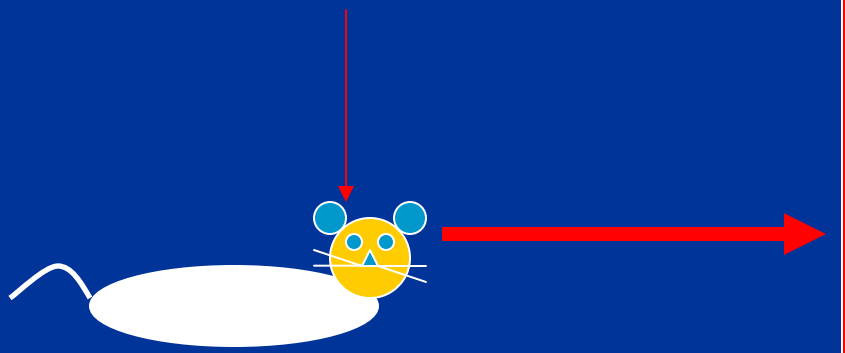
Molina-Infante et al, Clin Gastro Hepatol 2010
Dranove et al, JPGN 2010

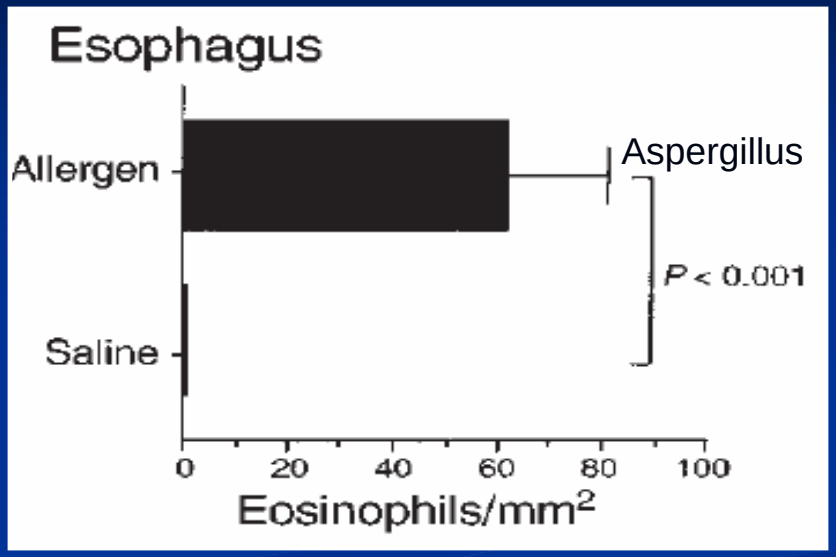
Triggers: Aeroallergens

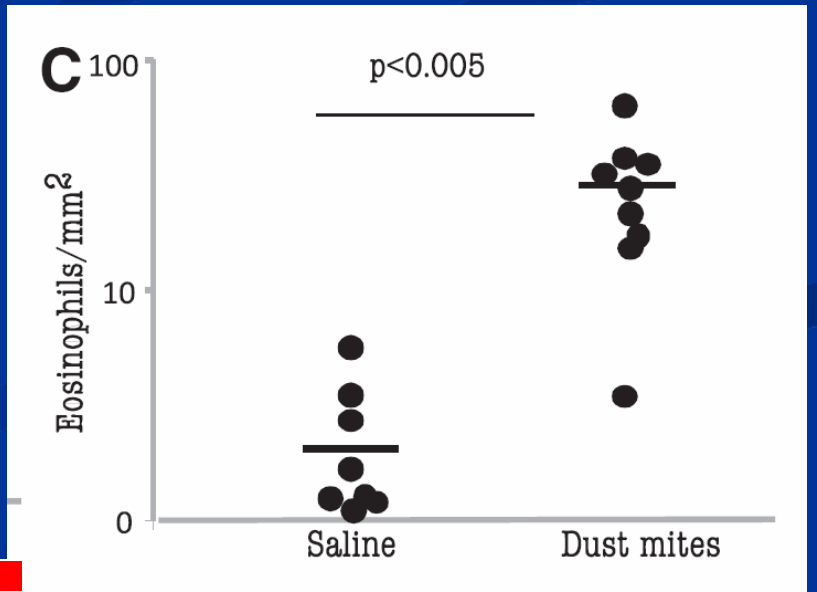
- Animal Models
- Human Disease

Aerollergens and EoE: Causal Link

- Instillation of:
- Intranasal Aspergillus
- Intranasal HDM
- Intranasal Cockroach
- Drives Murine EoE







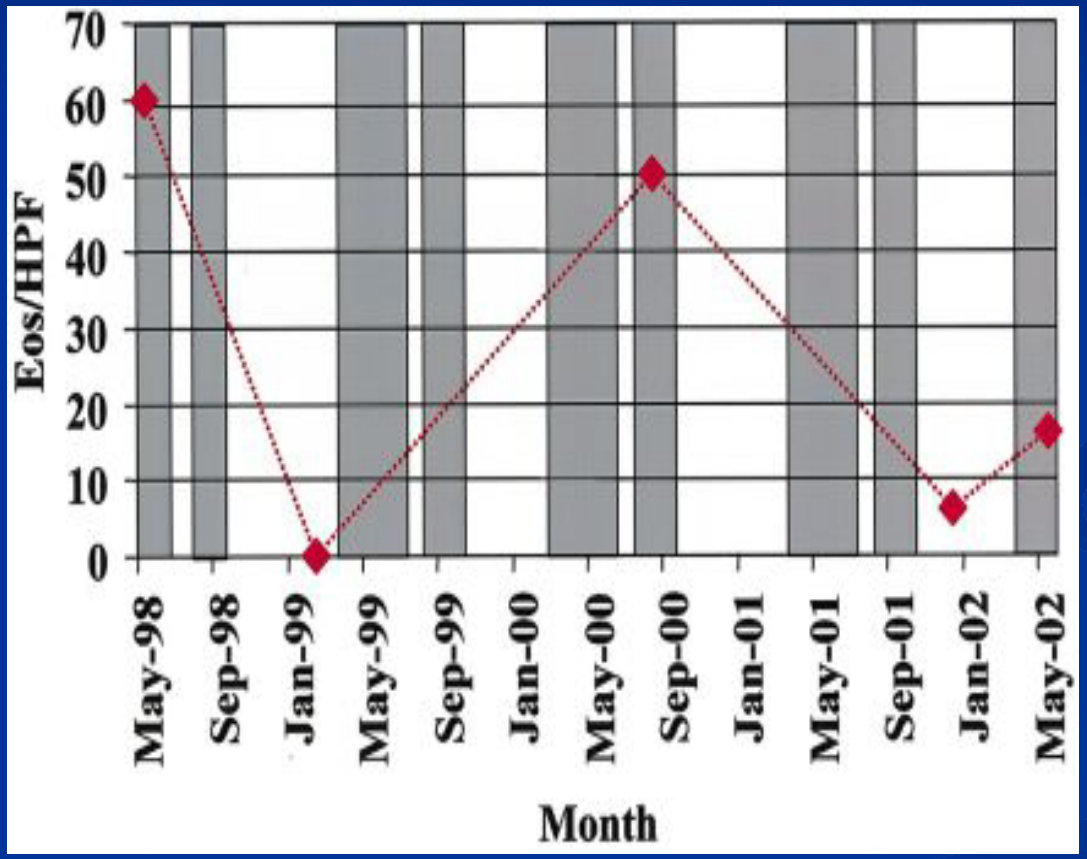
Mishra et al., J Clin Invest 2001
Rayapaudi et al, J Leuko Biol 2010

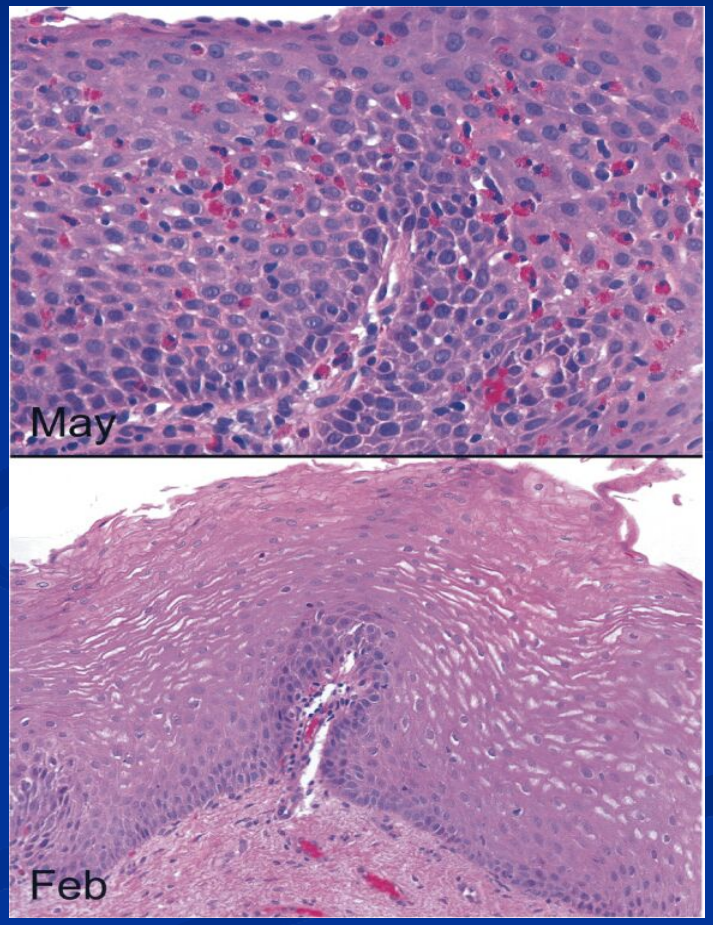
Pollen Driven Eosinophilia

Characteristic	Allergy	GERD	Normal
Any Esophageal Eos	10/38	5/24	0/25
Proximal Eos			
Num Pts	6	4	
Num Eos	5 +/- 7	2 +/- 1.7	
Range	1-20	1-4	
Distal Eos			
Num Pts	9	3	
Num Eos	3 +/- 4	8 +/- 6	
Range	1-12	3-14	

Onbasi et al. Clin Exp Allergy, 2005

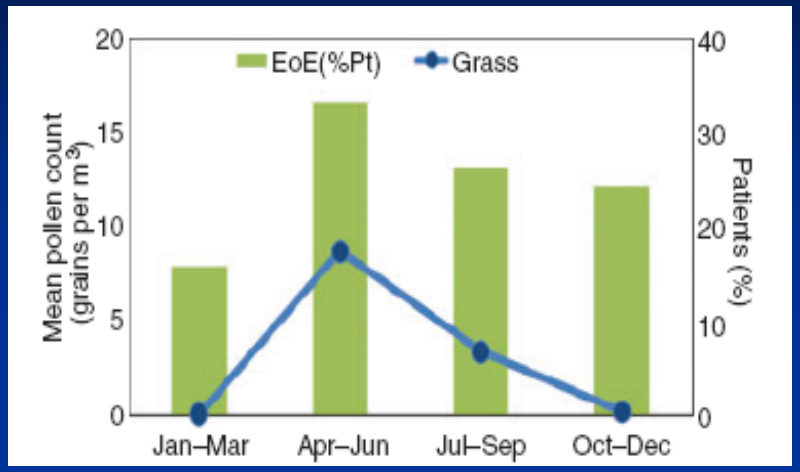
Pollens and EoE: Causal Link

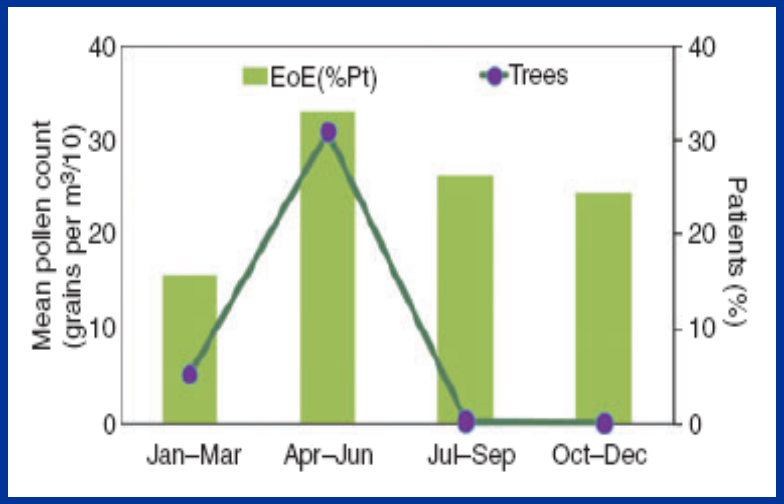


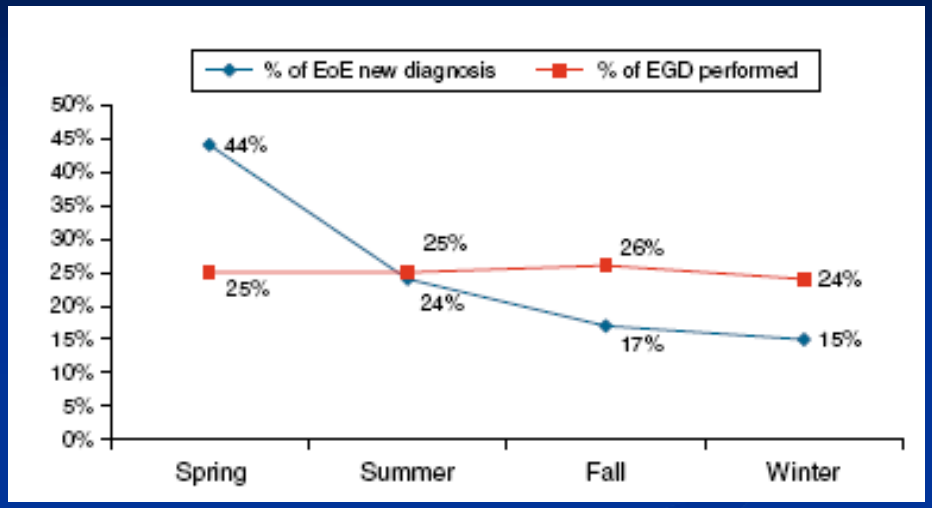


Fogg et al, JACI 2003

Seasonal EoE?







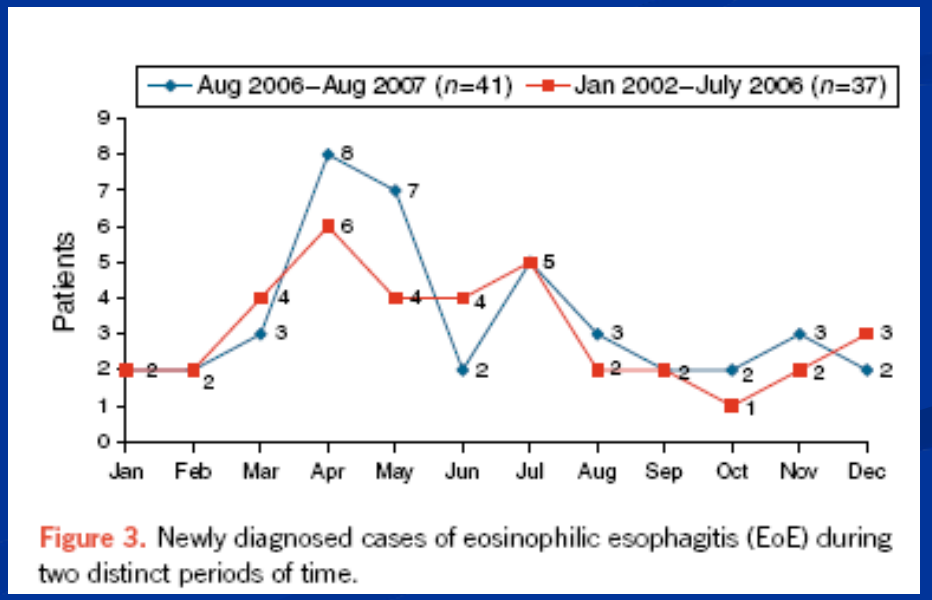


Figure 3. Newly diagnosed cases of eosinophilic esophagitis (EoE) during two distinct periods of time.

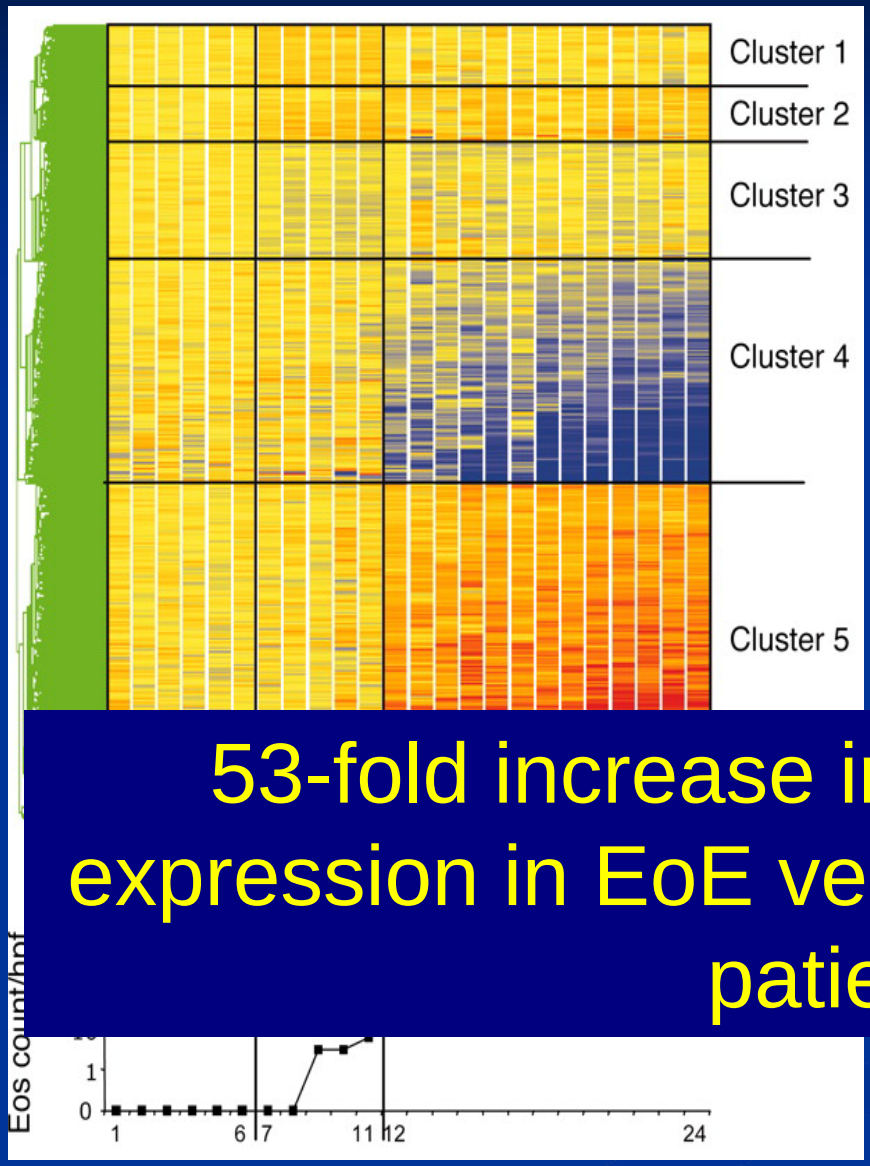
Moawad et al Alim Pharm Ther 2009

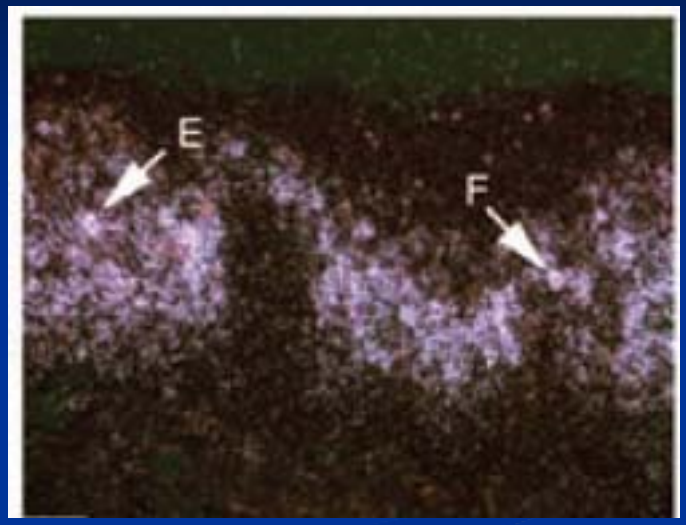
Almansa et al Am J Gastro 2009

Recruiting Eosinophils to the Esophagus

- Chemokines
- Interleukins
- Vascular Activation

Eotaxin-3



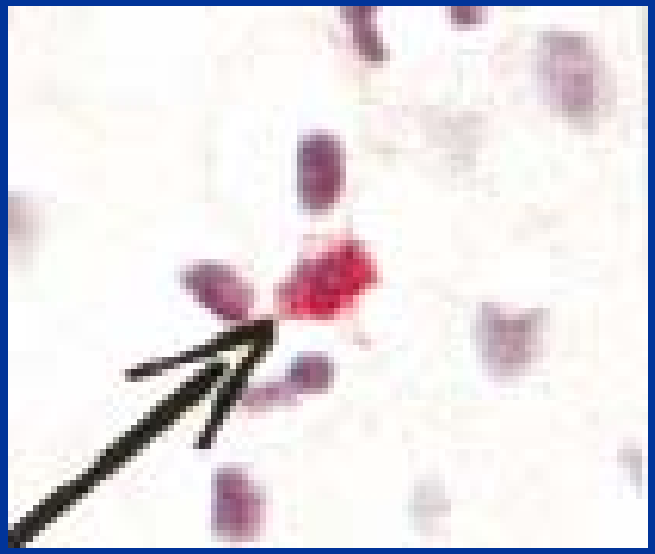


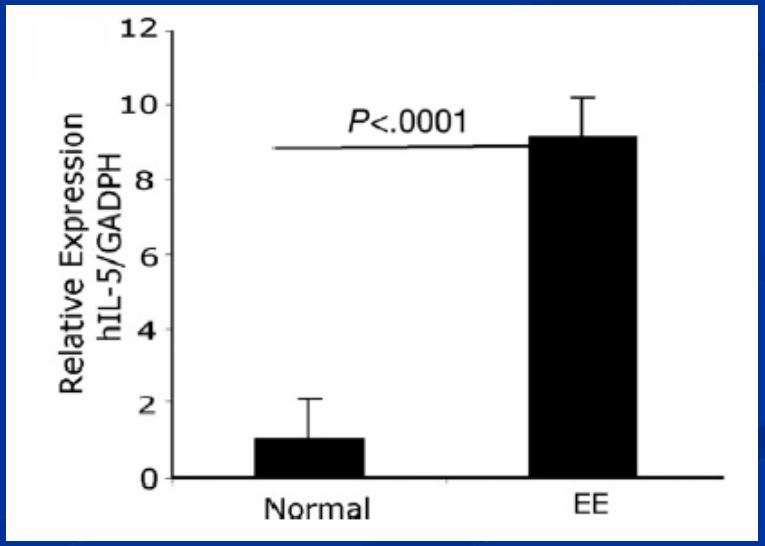
53-fold increase in Eotaxin-3 gene expression in EoE versus GERD pediatric patients

Blanchard, C. et al. J. Clin. Invest. 2006;116:536-547

IL-5

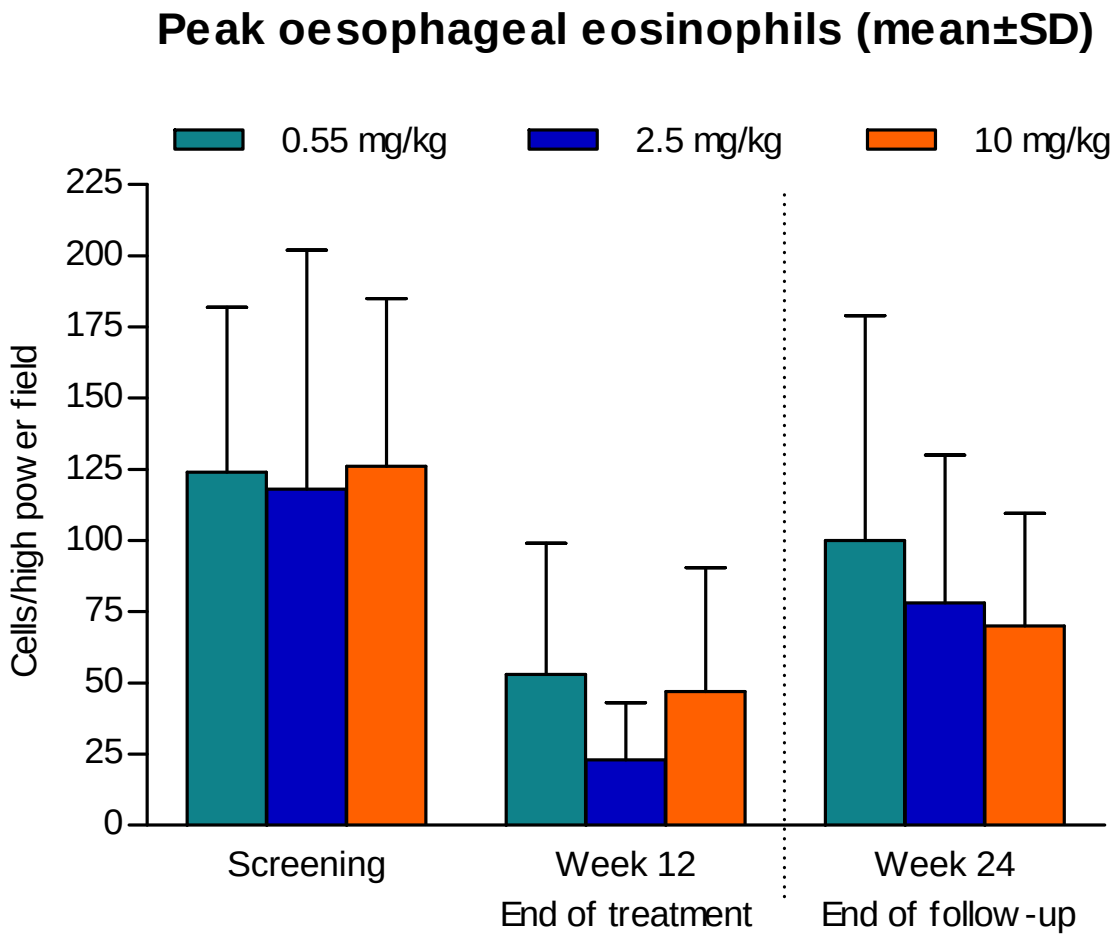
- EoE patients have Increased IL-5
- IL-5 Deficient Mice are Protected from EoE
- IL-5 miniosmotic pump promotes murine EoE



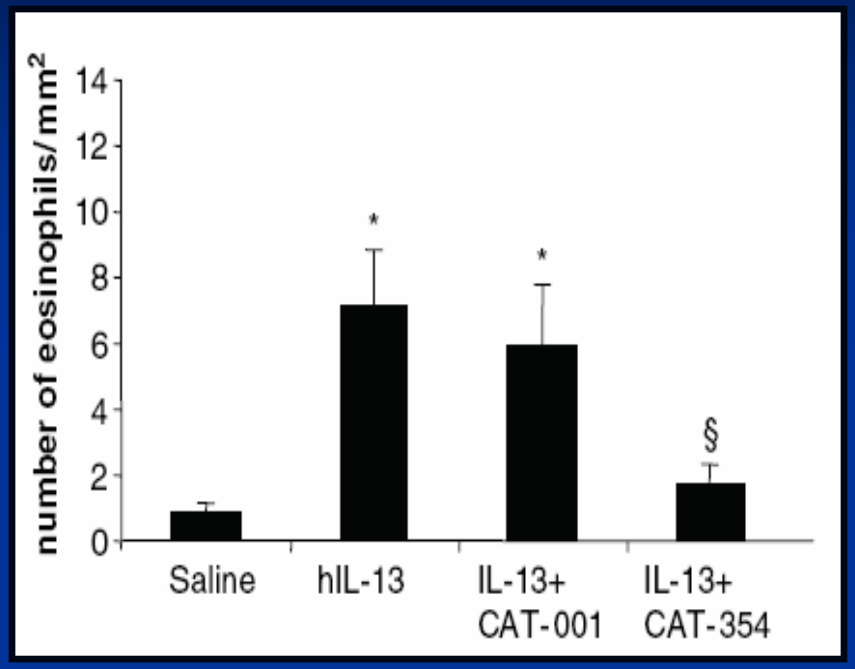


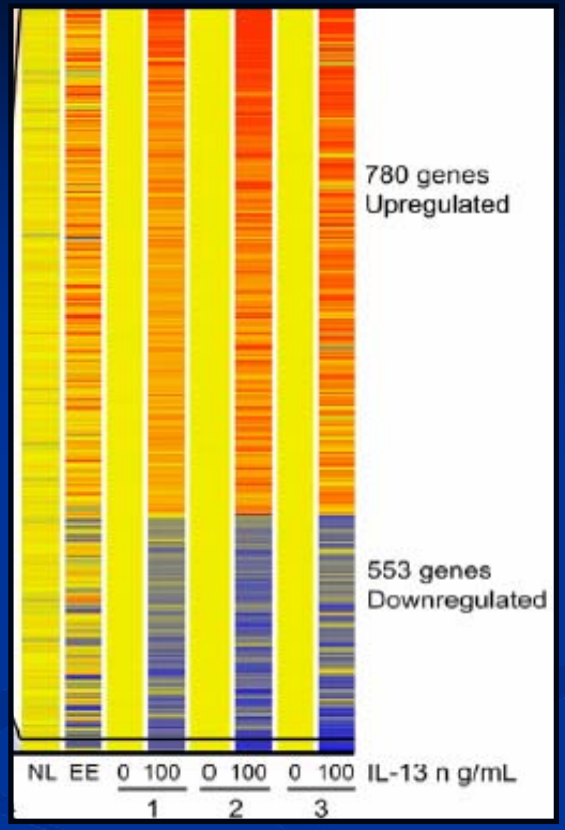
Straumann et al, JACI 2001
Mishra et al, 2008

Anti-IL-5 in Children



IL-13





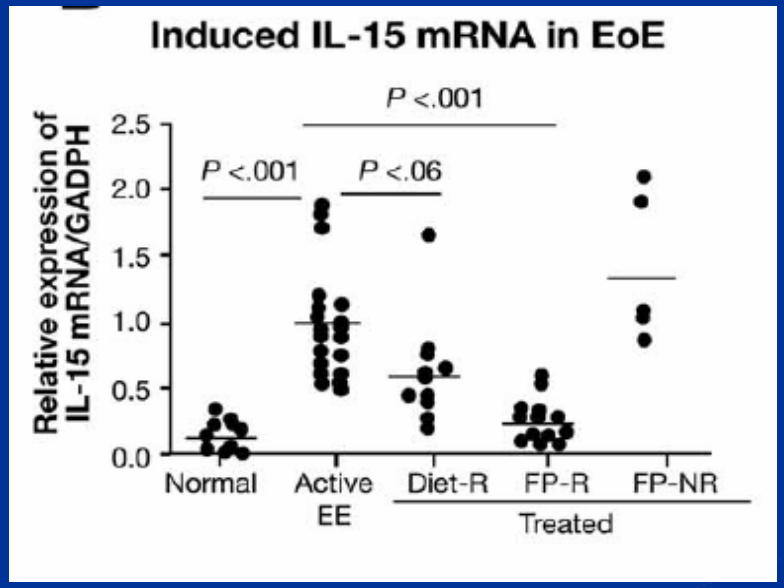
- Instilling IL-13 Causes Murine EE
- Resolved with anti-IL-13 Antibody

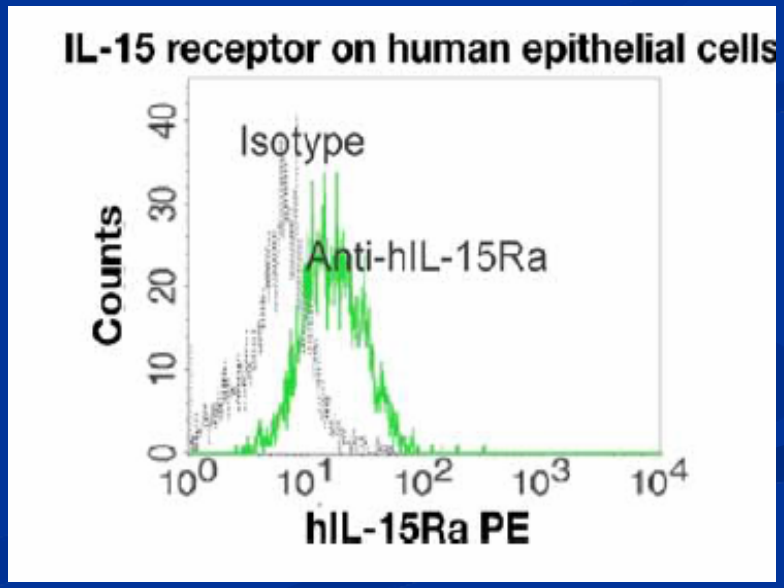
- IL-13 treatment promotes EoE transcriptome
- IL-13 induces the Eotaxin-3 promoter

Mishra & Rothenberg, Gastroenterology 2003
Blanchard et al, Clin Exp Allergy 2005

IL-15

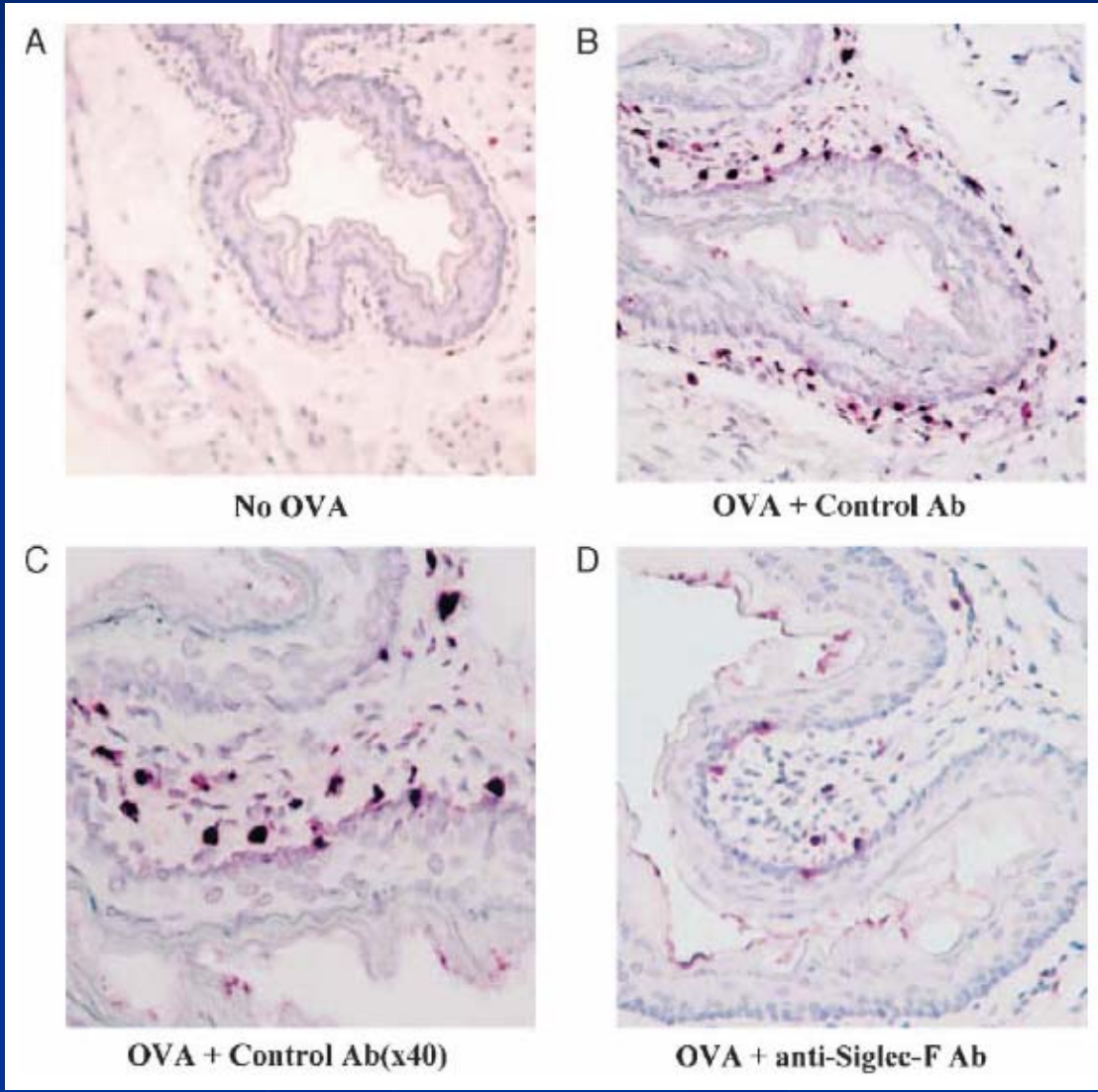
- Increased IL-15 on EoE Gene Chip
- IL-15Rα Deficient Mice: Protected from experimental EoE
- IL-15 Increased in Human Esophageal biopsies





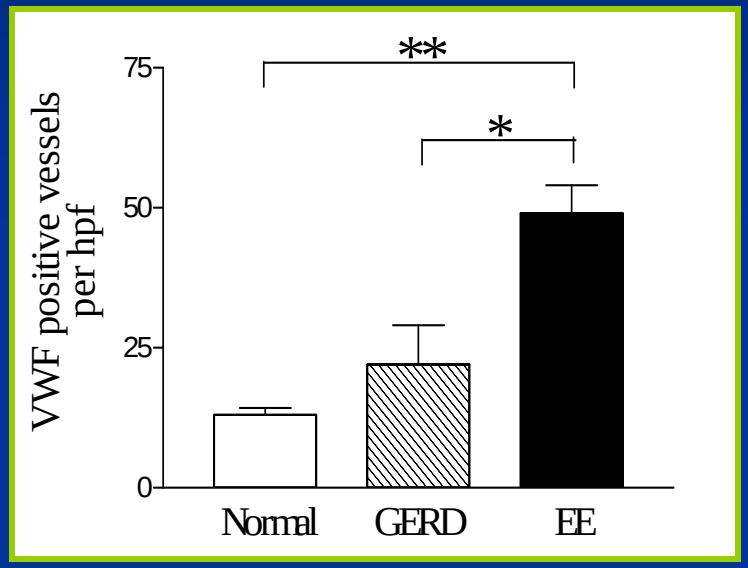
Rayapudi et al, Gastroenterology 2010

Siglecs and EoE

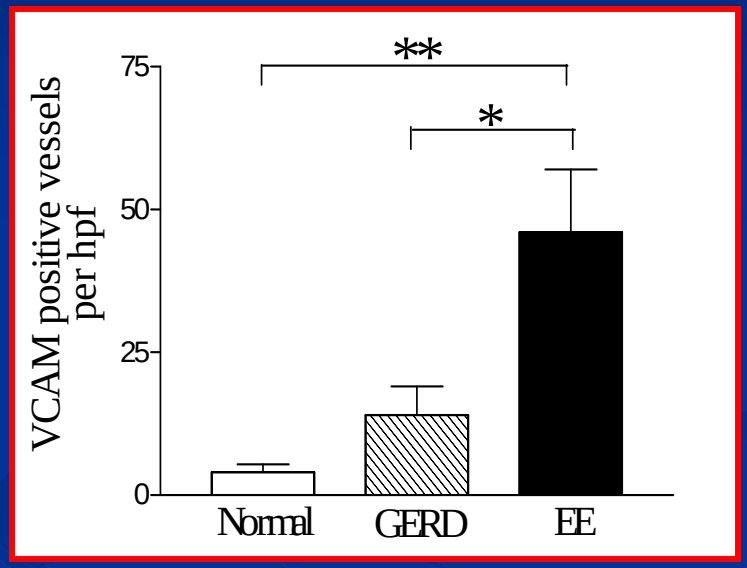


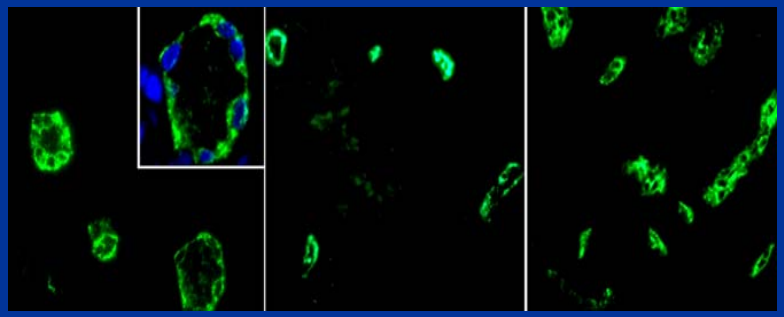
Esophageal Remodeling: Vascularity

vWF Positive Vessels

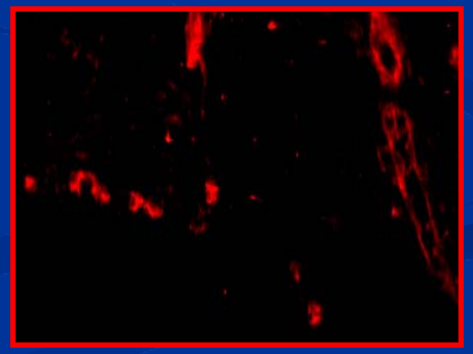


VCAM-1 Positive Vessels



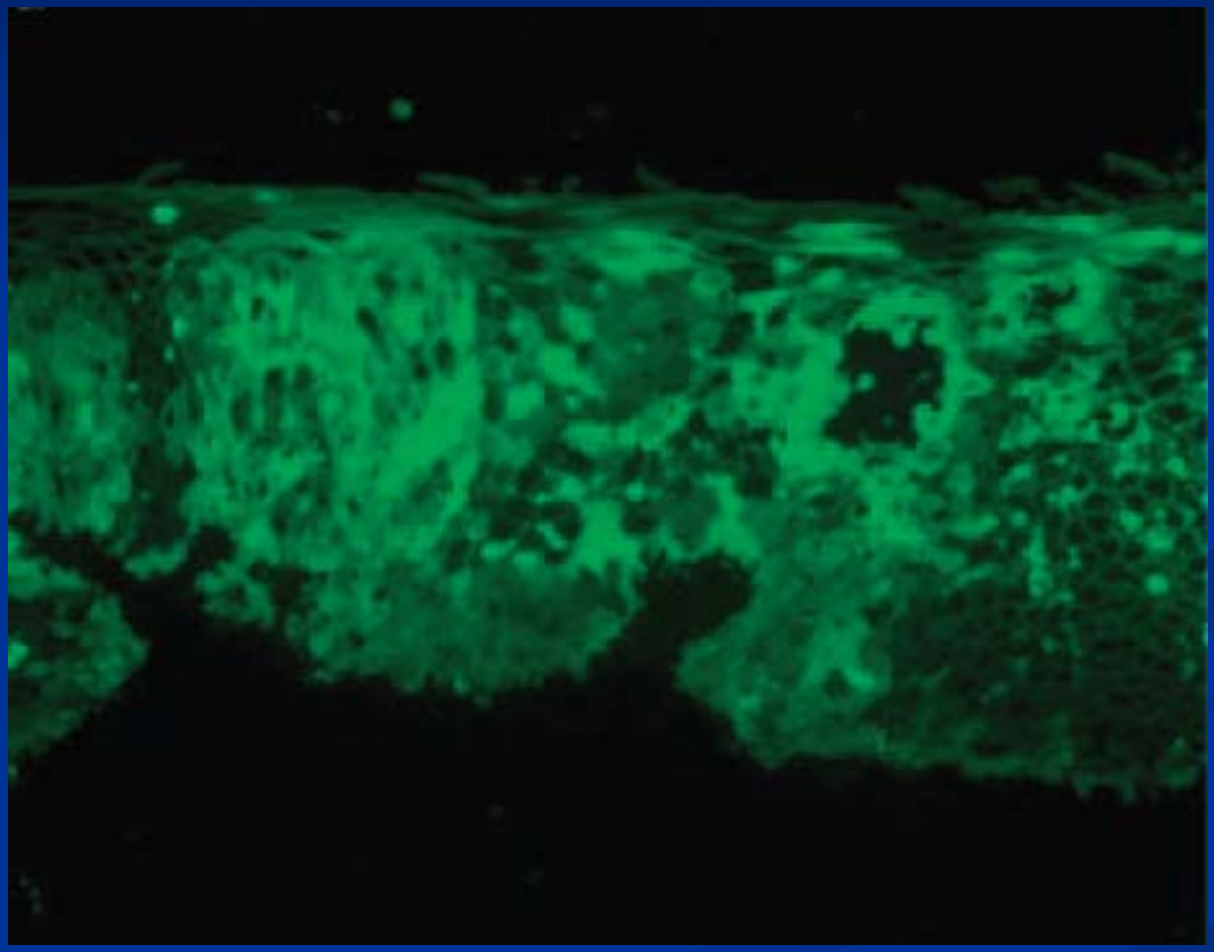


Normal GERD EE



Eosinophil Activation

Eosinophil Derived Neurotoxin



Kephart et al, Am J Gastro 2010

Major Basic Protein

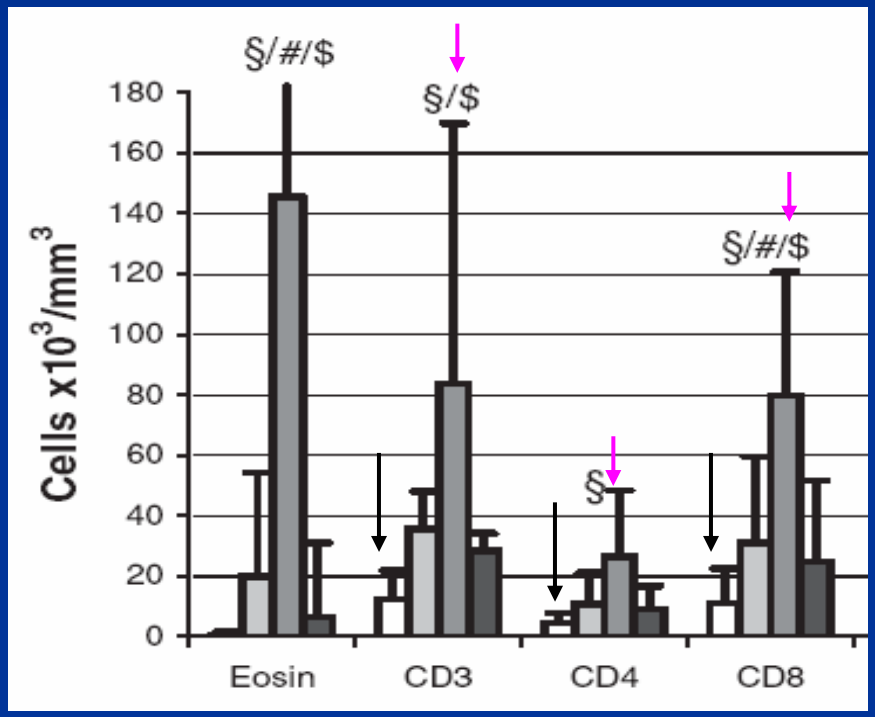
Mueller et al

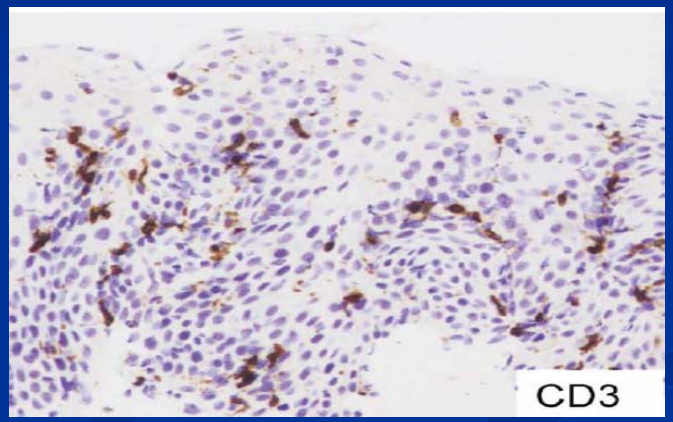
More Than Just Eosinophils

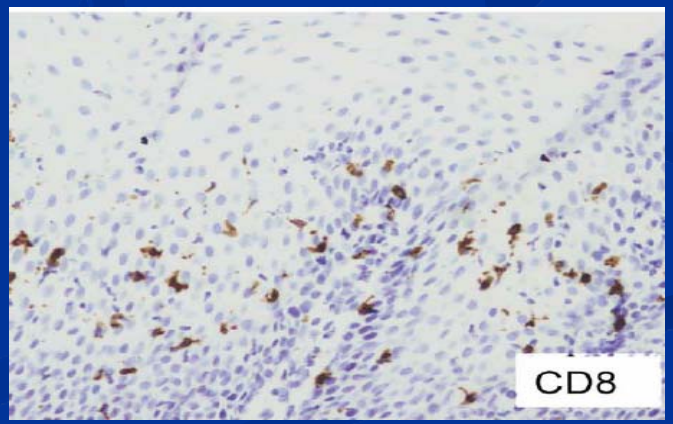
- T Cells
- B Cells
- TSLP

T Cells

- Increased CD3+, CD8+
- Murine EoE Induction Relies on T cells

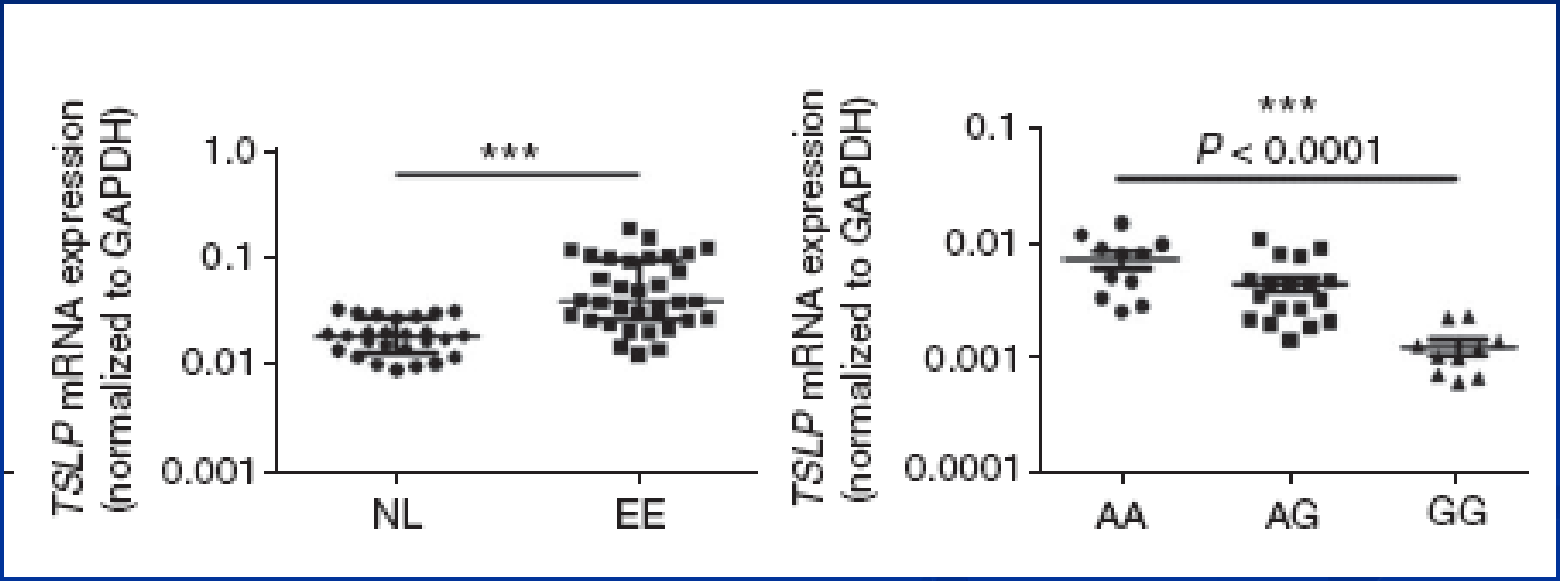






Lucendo et al, 2007; Mishra et al, 2007

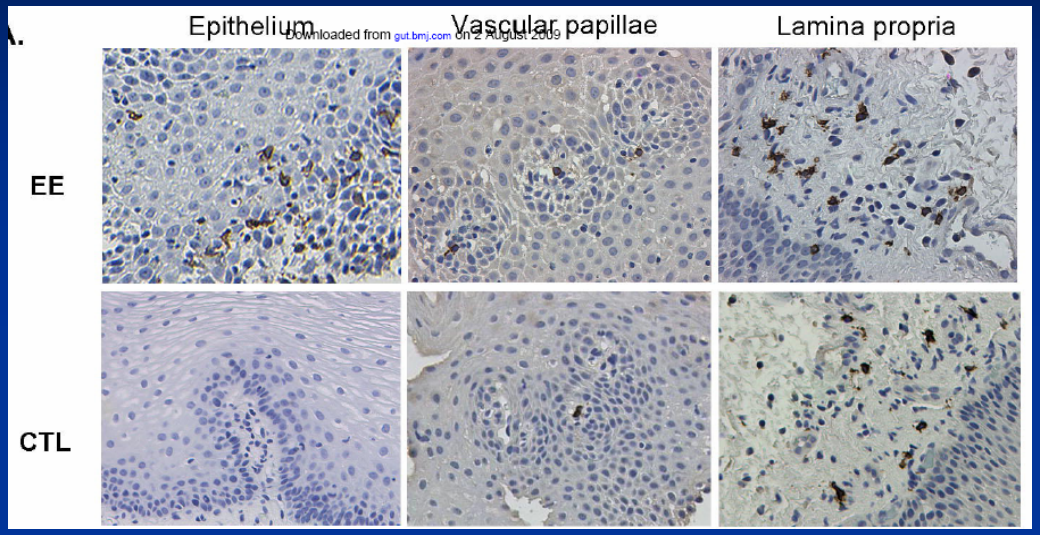
TSLP



- Increased TSLP expression in EoE
- Genetic variants in TSLP and Eotaxin-3 associate with EoE

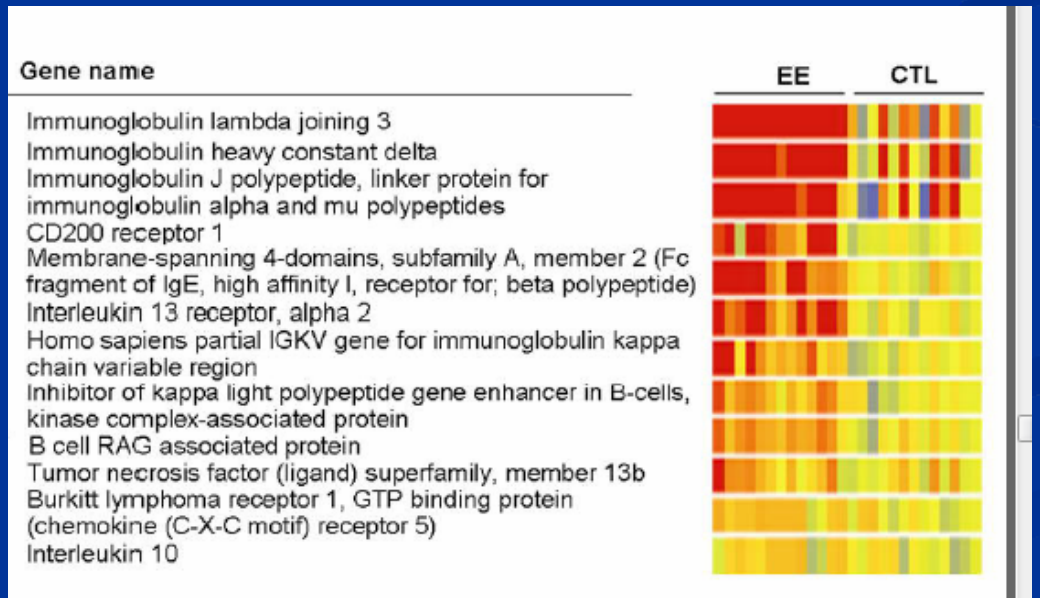
Rothenberg et al, Nature Genetics 2010

B Cells and Local IgE Production



Increased B cells in :

- Epithelium
- Vascular Papillae
- Lamina Propria



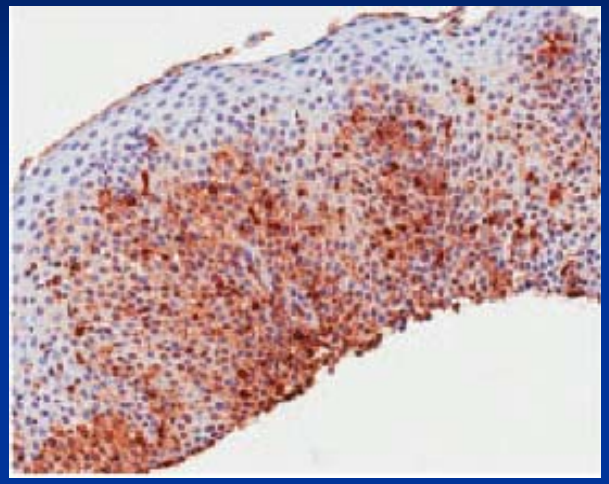
Increased IgE Class Switch Genes

Vicario et al, Gut 2009

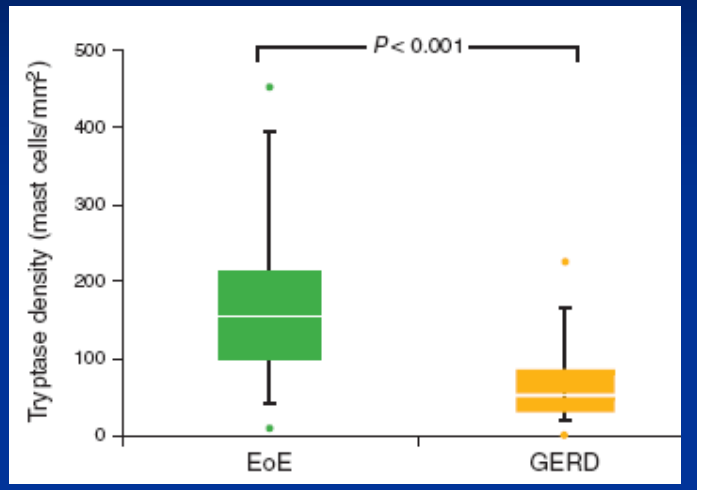
Mast Cells

Inflammation and Complications

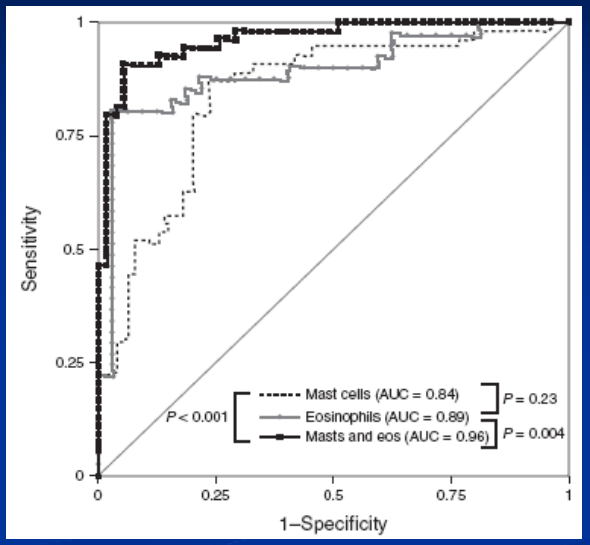
Mast Cells



Epithelial Tryptase



Mast Cells in EoE vs GERD

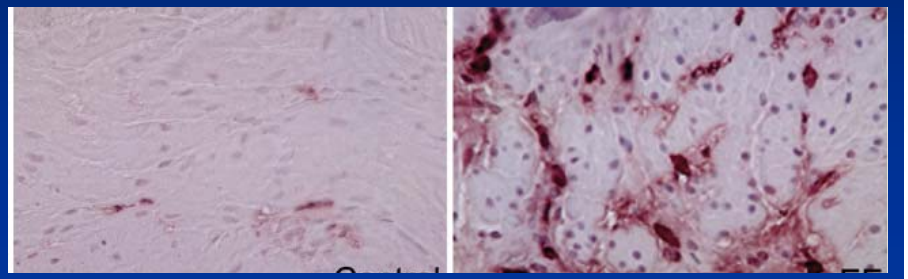


Diagnostic Implications

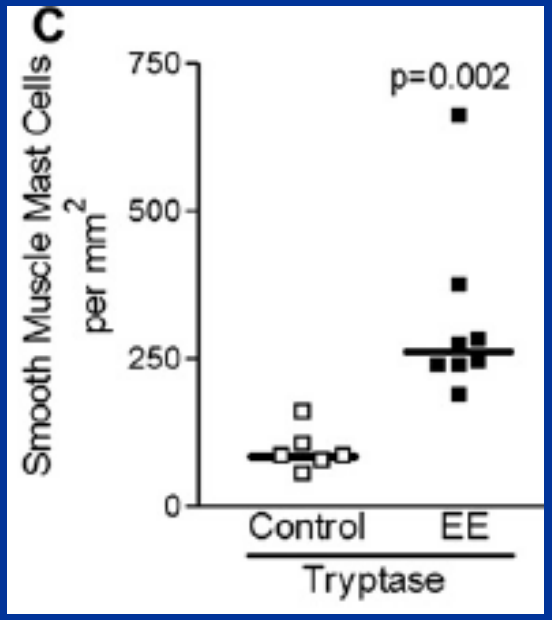
- Mast Cells: Elevated, Specific Gene Profile
- May help distinguish EoE from GERD

Dellon et al, Am J Gastro 2011
Abonia et al, JACI 2010

Smooth Muscle Inflammation



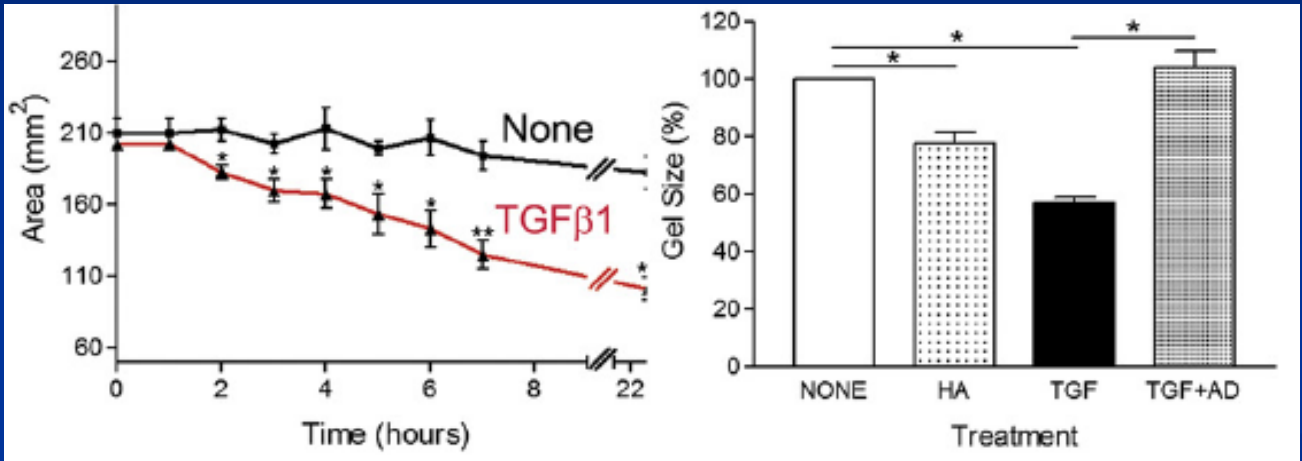
Control EoE



- Mast Cells are Increased in the Smooth Muscle
- Mast cells make TGFβ1

Aceves et al, JACI 2010

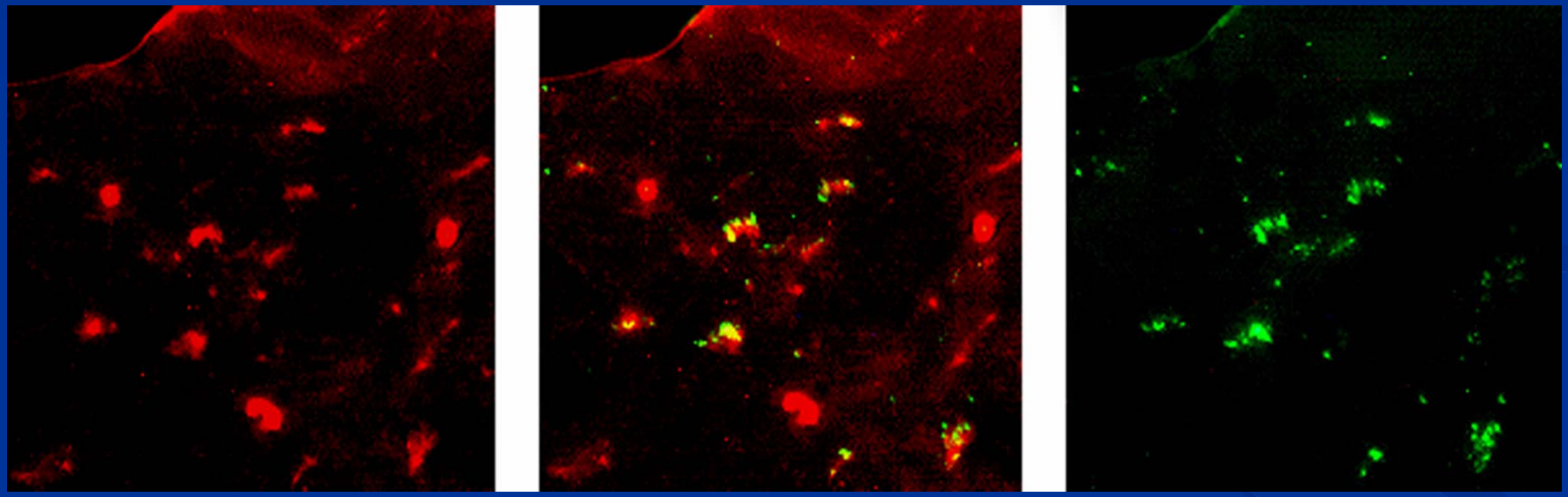
TGFβ1 Causes Smooth Muscle Contraction



- TGFβ1 induces esophageal smooth muscle cell contraction

Aceves et al, JACI 2010

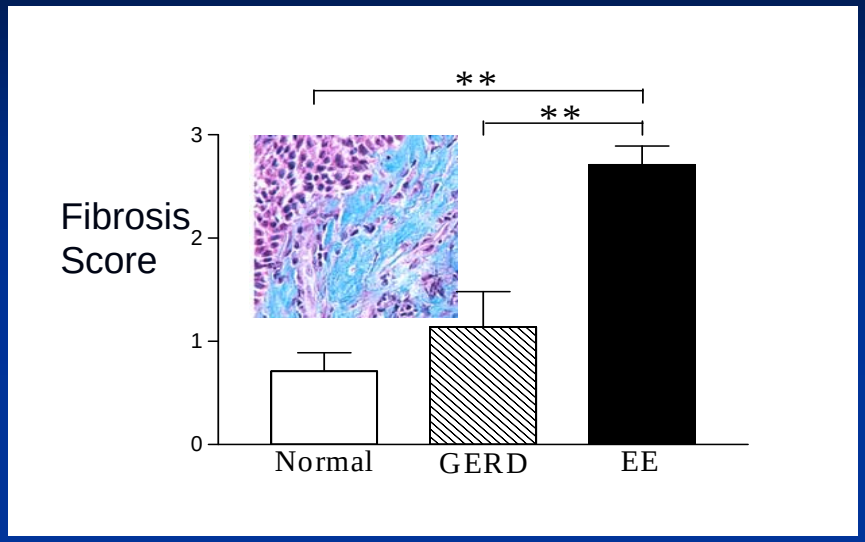
Esophageal Remodeling: Eosinophils Produce TGFβ1



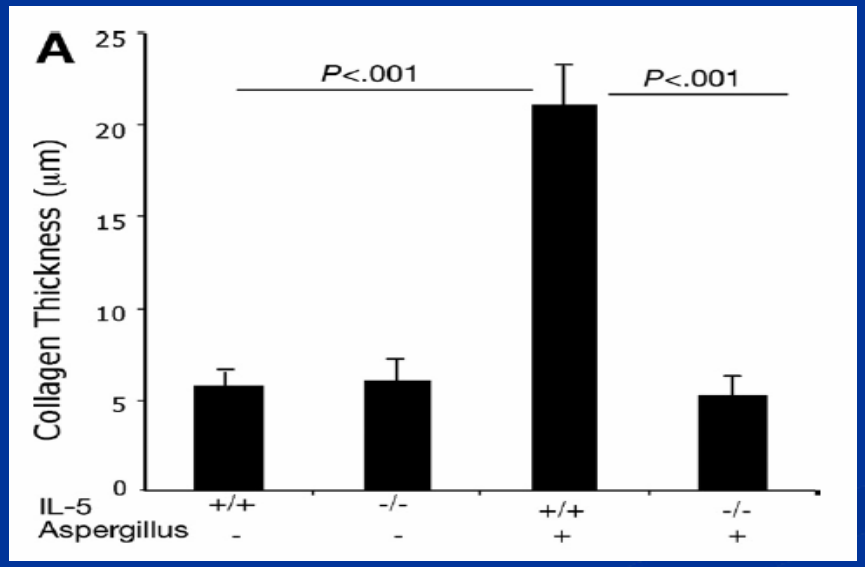
MBP | MBP + TGFβ1 | TGFβ1

Aceves et al, J All Clin Immunol 2007

Esophageal Fibrosis



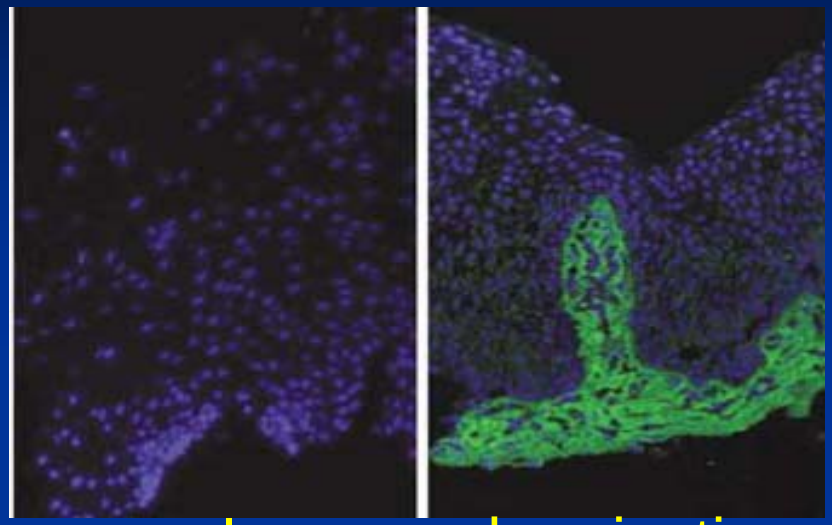
EoE Patients have Increased Fibrosis

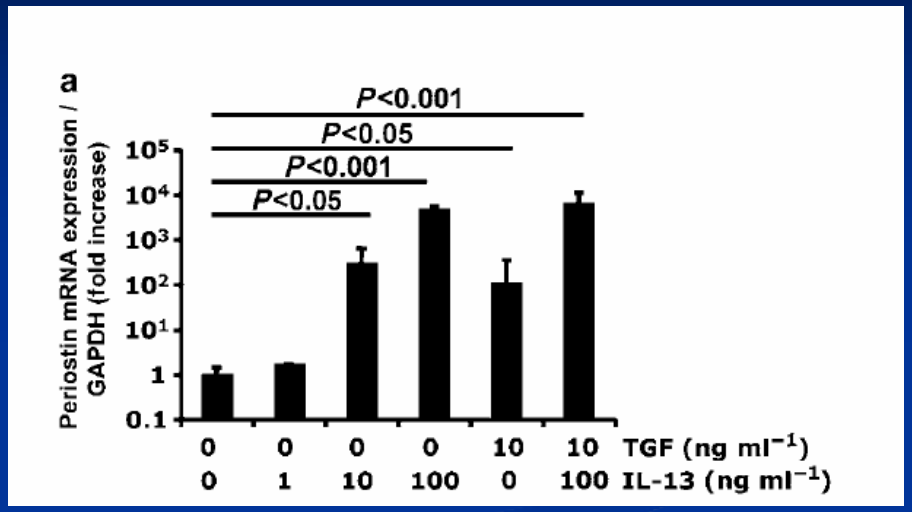


Animals without IL-5 and Eosinophils are Protected from Fibrosis

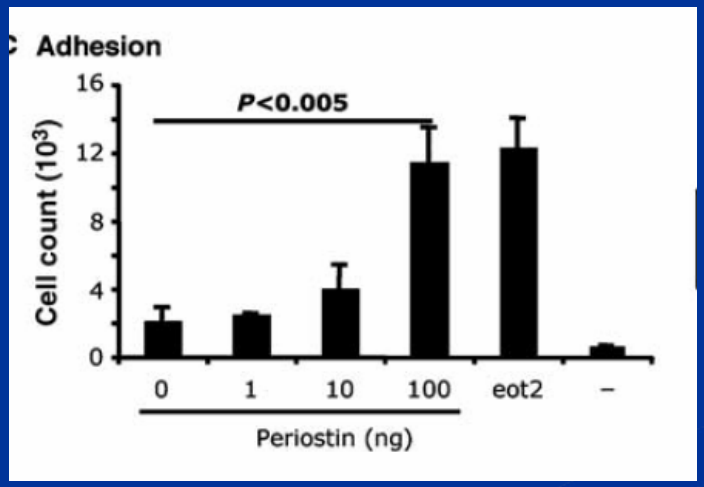
Aceves et al, JACI 2007
Mishra et al, Gastroenterology 2008

Esophageal Eosinophils: Periostin





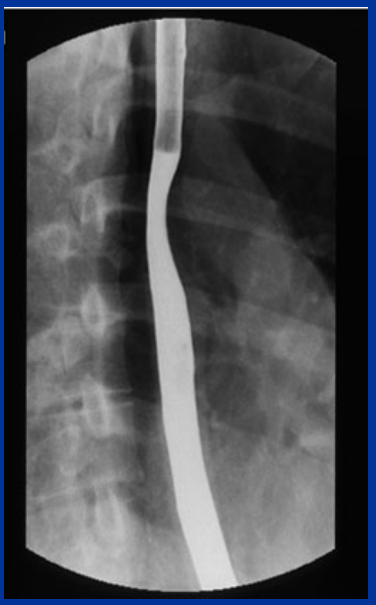
Increased periostin expression induced by TGFβ



Periostin increases eosinophil trafficking and adhesion

Blanchard et al, Mucosal Immunol 2008

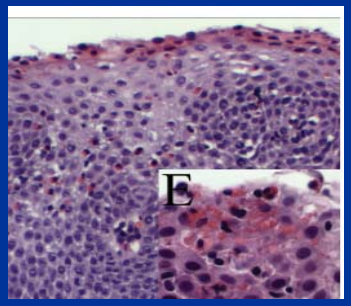
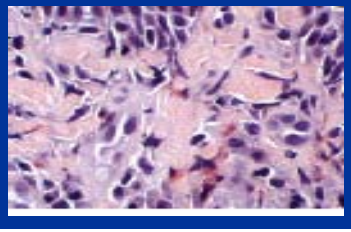
Esophageal Remodeling: The Key to the Pathogenesis of Complications?



Strictures
Dysmotility
Esophageal Rigidity
Food Impactions

GI Motility online (May 2006)

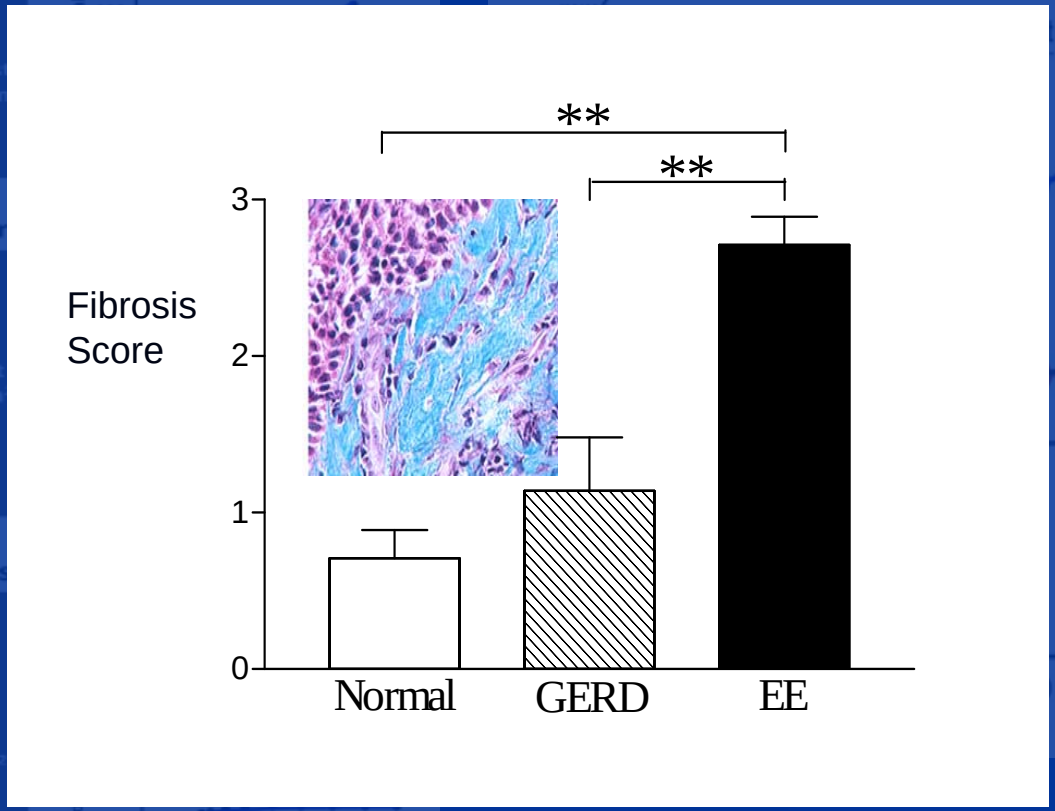
Inflammation Can Correlate with Endoscopy, Symptoms

Inflammation	Endoscopy	Symptom
<u>Epithelial:</u> Average Epithelial Score Prox+Mid+Distal 	Thickened/Furrows r=0.82* White Plaques, r =0.64* Pallor r=0.62* 	Dysphagia + Anorexia/Early Satiety r=0.32*
<u>Lamina Propria:</u> Fibrosis + Eosinophils 	Thickened/Furrows r=0.64* 	Dysphagia r= 0.45*

*p<0.05

Aceves et al, Annals of All Immunol 2009

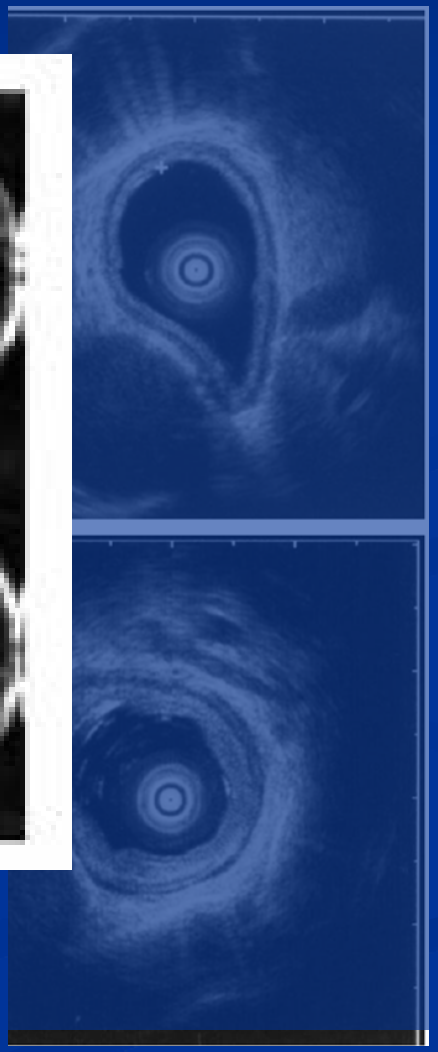
Decreased Esophageal Distensibility



Kwiatek et al, Gastroenterology 2011

Smooth Muscle

- Thickened esoph
- Dis-coordinated smooth muscle contraction
- Episodes of dysmotility correla with dysphagia



Nurko et al, Am J Gastro, 2009
Korsapaati et al, Gastroenterol 2009
Fox et al, Gastrointest Endosc, 2003

EGE: Beyond the Esophagus Different or Disease Extension?

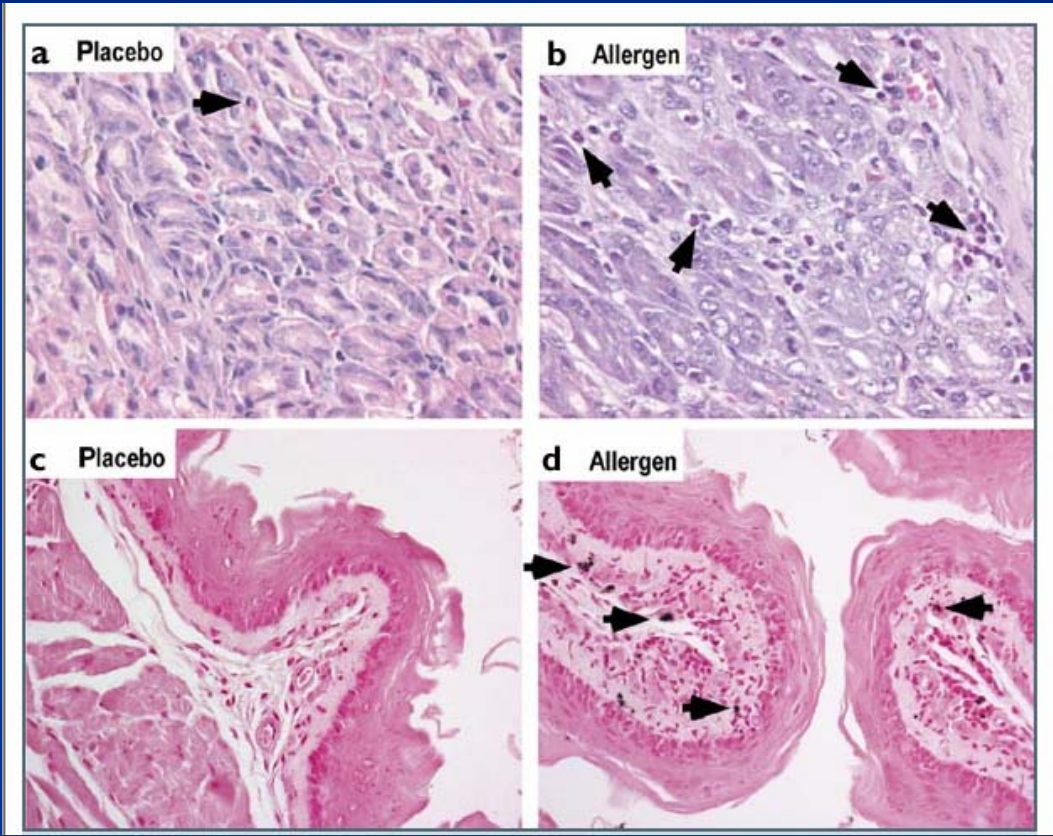
Eosinophilic Gastroenteritis

- Diagnostic criteria not established
  - Eosinophilia is normal in the non-esophageal intestine
- Often does not involve the esophagus
- Mucosal, Muscularis, Serosal Forms
- Primary – Atopic vs Non-atopic
- Secondary – Rule out
  - HES, Vasculitis
  - Celiac, IBD, Scleroderma, Infection

Eosinophilic Colitis

- Primary: Atopic vs Non-Atopic
  - Allergic Colitis of Infancy
- Secondary
  - HES, EGE
  - Rule out: IBD, Infection

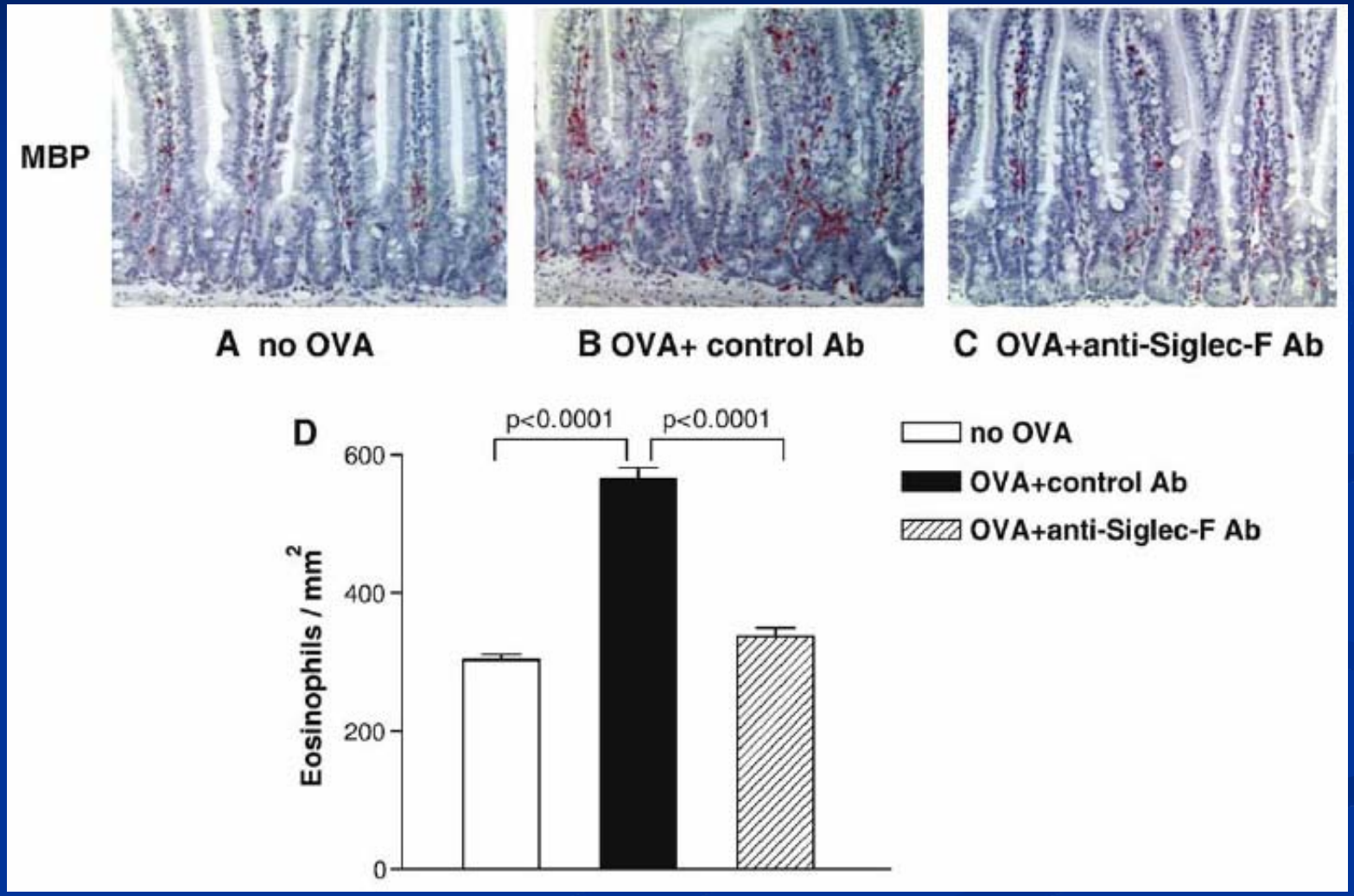
Animal Model of GI Eosinophilia



Ovalbumin induces Gastric and Esophageal Eosinophilia

Hogan et al, 2001

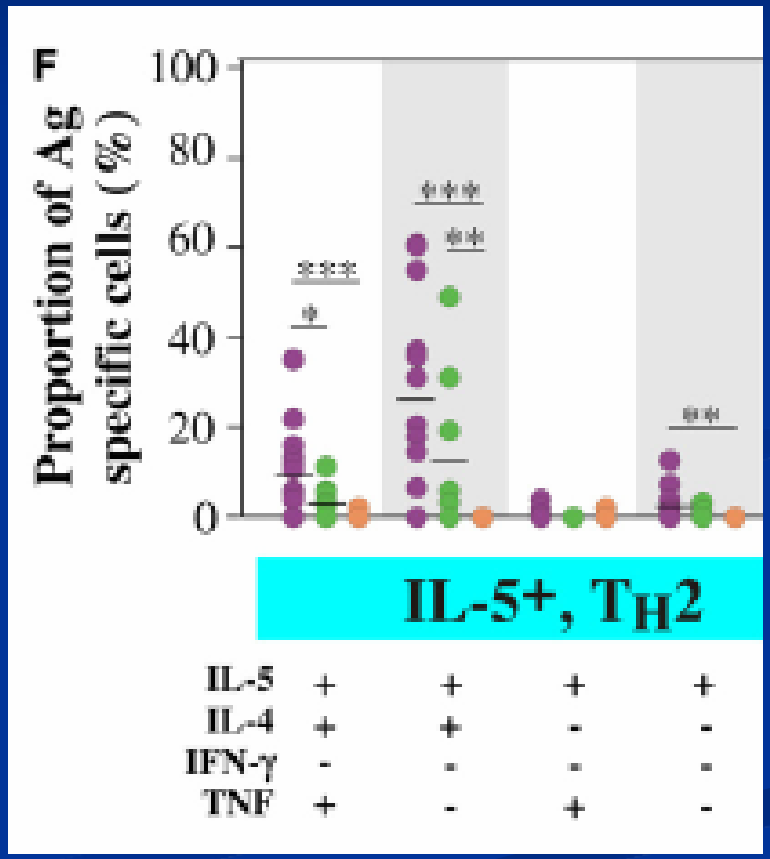
Animal Model of GI Eosinophilia



Song et al, Clin Exp Allergy 2008

Disease Mechanisms

- Increased CD4+ peripheral cells that are antigen specific
- Eosinophilic gastroenteritis patients have increased IL-5+,IL-4- cells compared to Non-allergic and Peanut Allergic Patients



Prussin et al JACI 2009

Conclusions

- Eosinophilic esophagitis is more than eosinophils
- Pathogenesis includes Eosinophil Activation
- Pathogenesis includes T cells, B cells, Mast Cells, and Degranulated Mast Cells
- Remodeling may explain the pathogenesis for Disease Complications
- EGE is likely a Distinct Disease from isolated EoE