



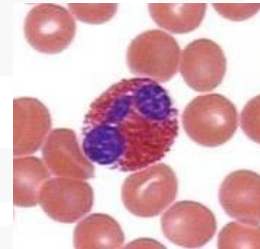
The Role of Allergy in Eosinophilic Esophagitis

Scott P Commins, MD, PhD



Learning Objectives

- Upon completion of this learning activity, participants should be able to define the clinical characteristics of Eosinophilic Esophagitis (EoE)
- Upon completion of this learning activity, participants should be able to identify relevant allergen testing in EoE
- Upon completion of this learning activity, participants should be able to design clinical treatment and management strategies for EoE



14 yo male seen for dysphagia

- Reports 2-3 years of intermittent sensation of food sticking above the suprasternal notch
- Might occur 1 x week but may have weeks without symptoms
- At times, he does induce emesis to clear food
- PMH: ASD, fish / shellfish allergy
- Family history: AR (father), depression, HTN
- Social: 7th grader, 1 cat at home, climbs trees

- GI Clinic

- » DDX

- Schatzki's ring
- Reflux esophagitis
- EoE
- motility problem

- » Plan

- omeprazole 20 mg before breakfast
- Barium swallow x-ray
- Upper endoscopy with biopsies in 4-6 weeks



14 yo male with dysphagia

- 2 weeks later swallow study performed and shows “poor clearance of the esophagus with primary and secondary waves. No anatomic abnormality. Further eval with manometry is suggested.”
- EGD was canceled by family due to “improvement” on omeprazole



15 yo male with dysphagia

- He re-presents to GI clinic 1.5 years later (now age 15 ½) with recurrent episodes of transient esophageal impaction – one episode stayed in esophagus overnight
- Stopped omeprazole over prior summer, about 4 months before food impaction
- Now placed on BID PPI with EGD planned in 6-8 weeks



15 yo male with dysphagia

- Prior to upper endoscopy, he was seen by otolaryngology for “obstructing tonsils” due to loud snoring x 2 years and waking with sensation of tonsil blocking his swallowing
- After 3 months on BID PPI, he has tonsillectomy and EGD w biopsy (in March):
 - » Proximal: increased intraepithelial eosinophils up to 62 eos/HPF with eosinophilic microabscesses
 - » Distal: up to 21 eos/HPF
 - » Plan – swallowed fluticasone and allergy referral
 - Stop PPI



- Peds Allergy eval
 - » Noted he had angioedema to fish / shellfish that was treated with diphenhydramine and avoidance diet
 - » History of SAR – worse in spring
 - » Has 1 dog and 1 cat, which sleeps in his bed
 - » History of eczema as a child (no treatment currently)
 - » Eating soup and apple for lunch
 - » Skin prick testing was performed



Skin Testing

	ALLERGEN	Wheal (mm)	Flare (mm)
1	Saline	0	0
2	Cat	2	12
3	Dog Dander (Hollister)	2	20
4	Dust Mite Mix	0	0
5	Cockroach Mix	0	0
6	Elm Mix	0	0
7	Hickory – Pecan Mix	0	0
8	Oak Mix	12	40
9	Ash Mix	13	45
10	Birch Mix	4	30
11	Maple Mix	0	0
12	Poplar, White	0	0
13	Sycamore, Eastern	10	25
14	Black Walnut	7	30
15	Black Willow	5	35
16	Cedar, Red	2	15

	ALLERGEN	Wheal (mm)	Flare (mm)
17	Cocklebur	3	12
18	Lamb's Quarter	10	40
19	Rough Pigweed	6	30
20	Ragweed Mix	10	35
21	Plantain – Sorrel Mix	8	22
22	Mugwort, Common	15	45
23	Baccharis	3	18
24	Grass Mix 7	15	40
25	Bermuda	20	45
26	Johnson	15	45
27	Aspergillus Fumigatus	2	20
28	Alternaria alternata	10	35
29	Cladosporium	0	0
30	Penicillium mix	0	0
31	Histamine	5	45



- Peds Allergy eval
 - » Noted he had angioedema to fish / shellfish that was treated with diphenhydramine and avoidance diet
 - » History of SAR – worse in spring
 - » Has 1 dog and 1 cat, which sleeps in his bed
 - » History of eczema as a child (no treatment currently)
 - » Eating soup and apple for lunch
 - » Skin prick testing was performed
 - » Plan
 - daily oral anti-histamine
 - Nasal steroid spray
 - Avoid wheat and dairy
 - Referral to adult GI EoE specialist



- Adult GI EoE specialist
 - » Agrees with Peds A/I eval that no need for PPI or topical corticosteroid (tCS)
 - » Try dietary changes and make nutrition referral
- After 2 months on dairy / wheat elimination diet, EGD is performed (in August)
 - » Proximal: 90 eos/HPF
 - » Distal: 45 eos/HPF
 - » PLAN – increase avoidance to dairy, wheat, egg and soy elimination diet (already avoids fish / shellfish)
 - Repeat EGD in 6 weeks



16 yo male with dysphagia

- Adult GI EoE specialist
 - » 2 months later (October), EGD:
 - No symptom response
 - Proximal: 180 eos/HPF
 - Distal: 10 eos/HPF
 - » PLAN – increase to 6FED x 6 weeks and re-biopsy



- Adult GI EoE specialist
 - » 2 months later (October), EGD:
 - No symptom response
 - Proximal: 180 eos/HPF
 - Distal: 10 eos/HPF
 - » PLAN – increase to 6FED x 6 weeks and re-biopsy
- Follow-up EGD
 - » Again, no symptomatic response
 - » Proximal: 140 eos/HPF
 - » Distal: 60 eos/HPF
 - » PLAN – topical CS & referral to Adult A/I



- Adult A/I eval
 - » Since no improvement with 6FED, he was eating “whatever he wants” and reported “significant” seasonal AR symptoms: sneezing, rhinorrhea, nasal itch, ocular itching
 - » Planned EGD 2 weeks later on tCS:
 - Improved symptomatically
 - Proximal: 60 eos/HPF
 - Distal: 32 eos/HPF
 - Serum IgE testing during EGD procedure



Serum IgE Testing

Cod Fish IgE	1.09*
Shrimp IgE	2.98*
Milk (Cow) IgE	<0.35
D. farinae IgE	0.67*
D. pteronyssinus IgE	0.50*
Cat dander IgE	1.63*
Dog dander IgE	1.14*
Bahia Grass IgE	20.4*
Bermuda Grass IgE	19.8*
Meadow Fescue Grass IgE	42.8*
Johnson Grass IgE	13.0*
Timothy Grass IgE	39.6*
Orchard Grass IgE	40.3*
Alternaria IgE	4.49*

White Ash tree IgE	26.1*
Beech (American) tree IgE	22.4*
Birch tree IgE	21.1*
Box Elder tree IgE	6.89*
Cottonwood (White Poplar)	12.6*
Elm tree IgE	18.5*
Maple Leaf Sycamore IgE	11.8*
White Oak tree IgE	22.9*
Pecan Hickory IgE	39.5*
Walnut tree IgE	21.5*
Ragweed, short (common)	11.8*
English Plantain IgE	10.6*
Pigweed, Common IgE	9.09*
Sheep Sorrel IgE	9.31*
Mugwort IgE	7.52*
Goosefoot (Lamb's Quarter)	7.48*
Goldenrod IgE	8.35*
Cocklebur IgE	2.24*



- Adult A/I eval
 - » Start immunotherapy under SAR diagnosis
 - » EGD 4 months later
 - Proximal: 0 eos/HPF
 - Distal: 48 eos/HPF
 - Reported “some” symptoms
 - » EGD after 5 months on maintenance IT
 - Symptom-free
 - Proximal: 0 eos/HPF
 - Distal: 5 eos/HPF



- Adult A/I eval follow-up
 - » Continued immunotherapy with much improved SAR symptoms
 - » EGD after 10 months on maintenance IT
 - Proximal: 0 eos/HPF
 - Distal: 2 eos/HPF
 - No food avoidance other than fish / shellfish
 - No PPI, no tCS



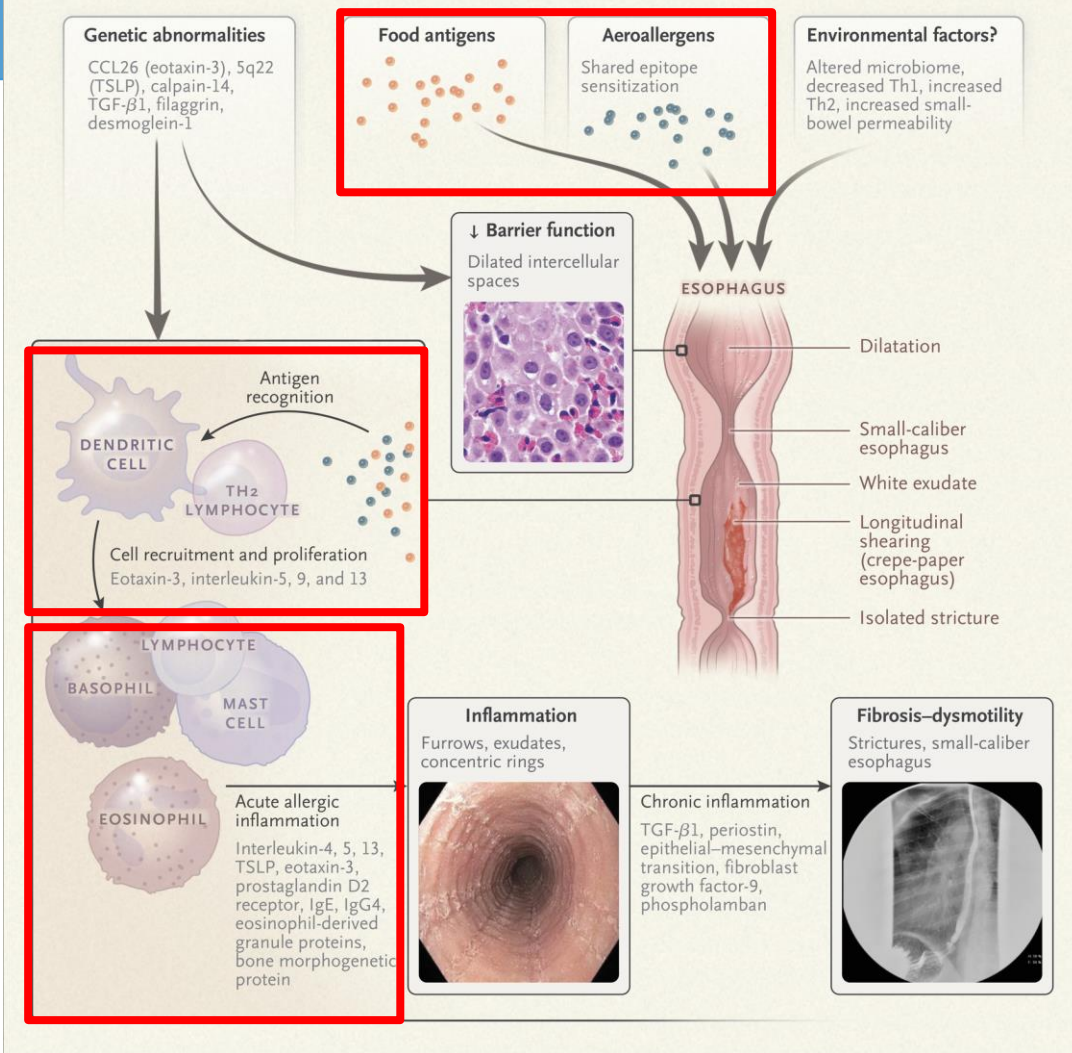
Pathogenesis of EoE

**Chronic Ag
exposure**

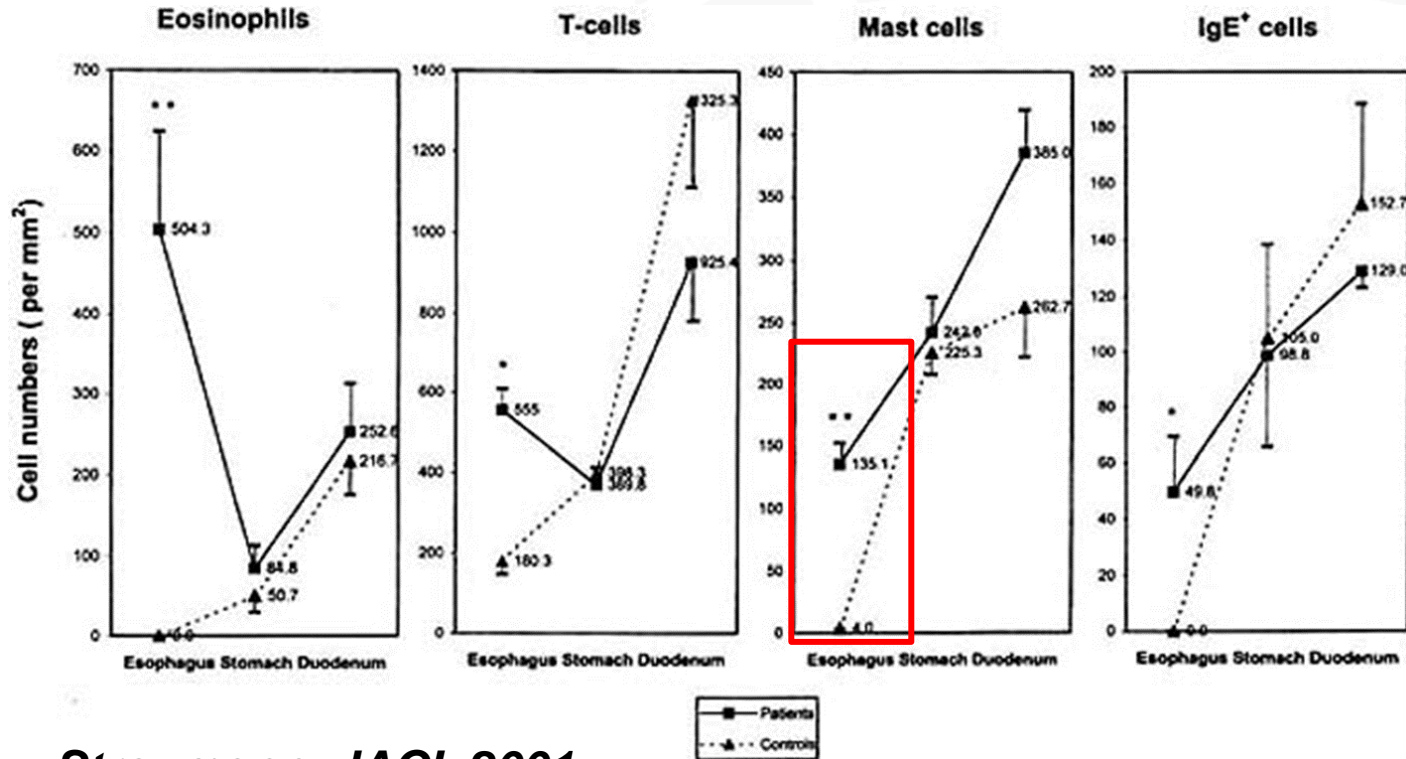


**Th2
coordinated
response**

*Furuta & Katzka,
NEJM 2015*

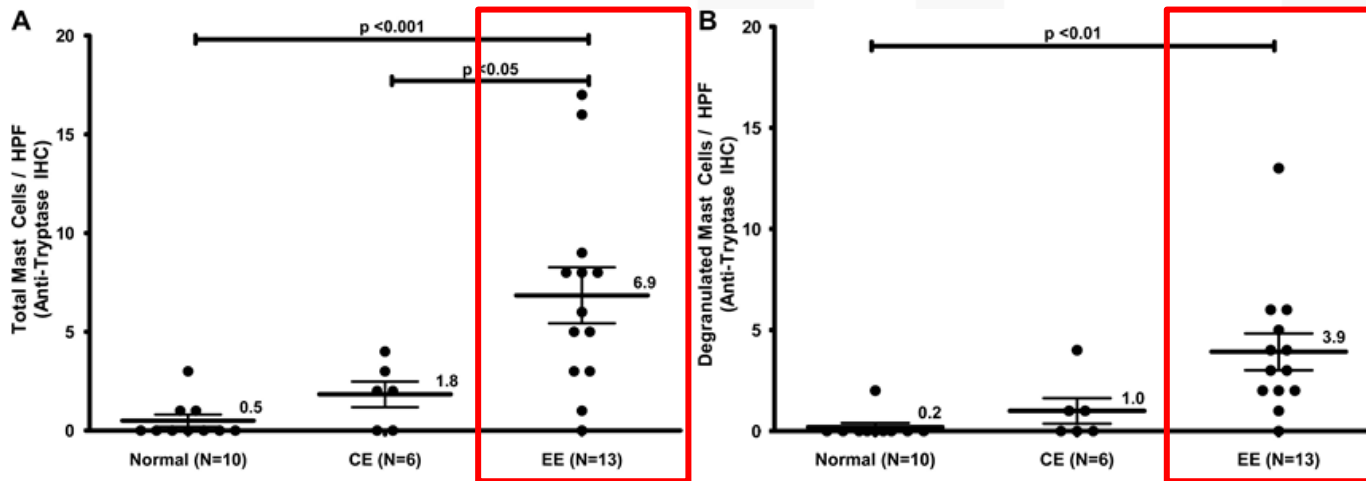


Th2-type associated inflammation in EoE



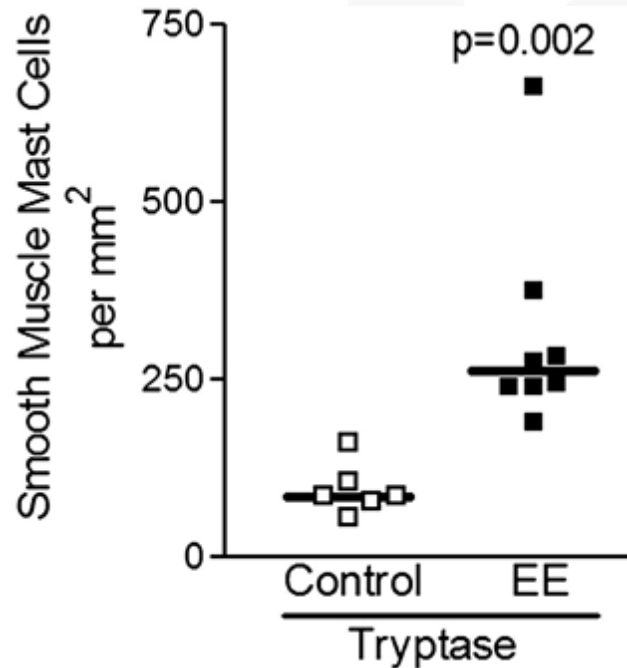
Straumann, JACI, 2001

Activated mast cells are increased in EoE and differentiate from other types of esophagitis



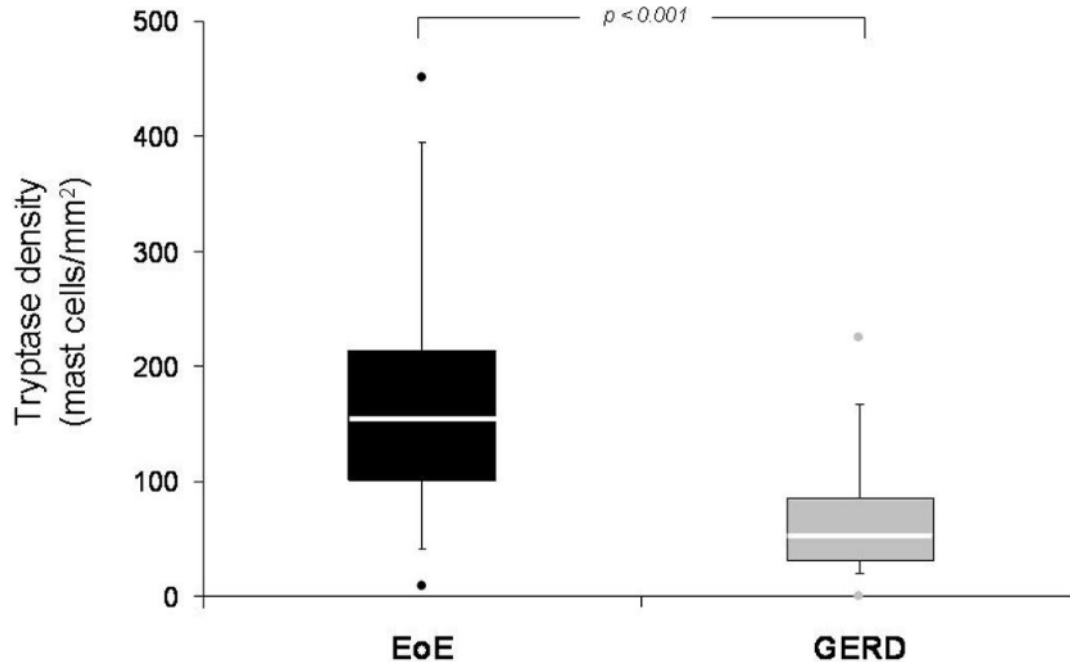


Activated mast cells are increased in EoE and differentiate from other types of esophagitis

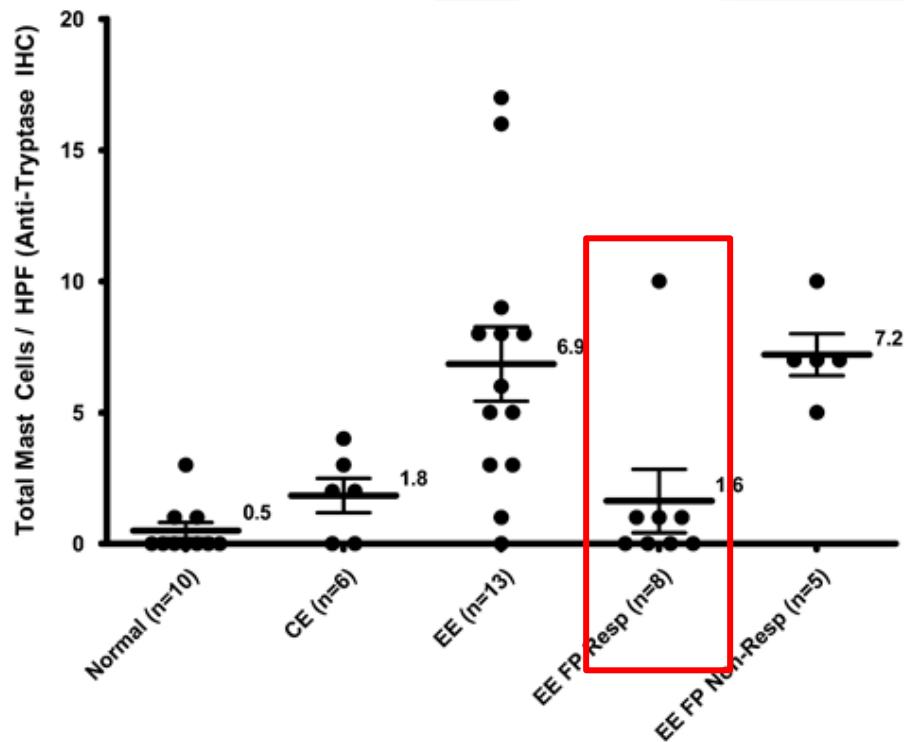




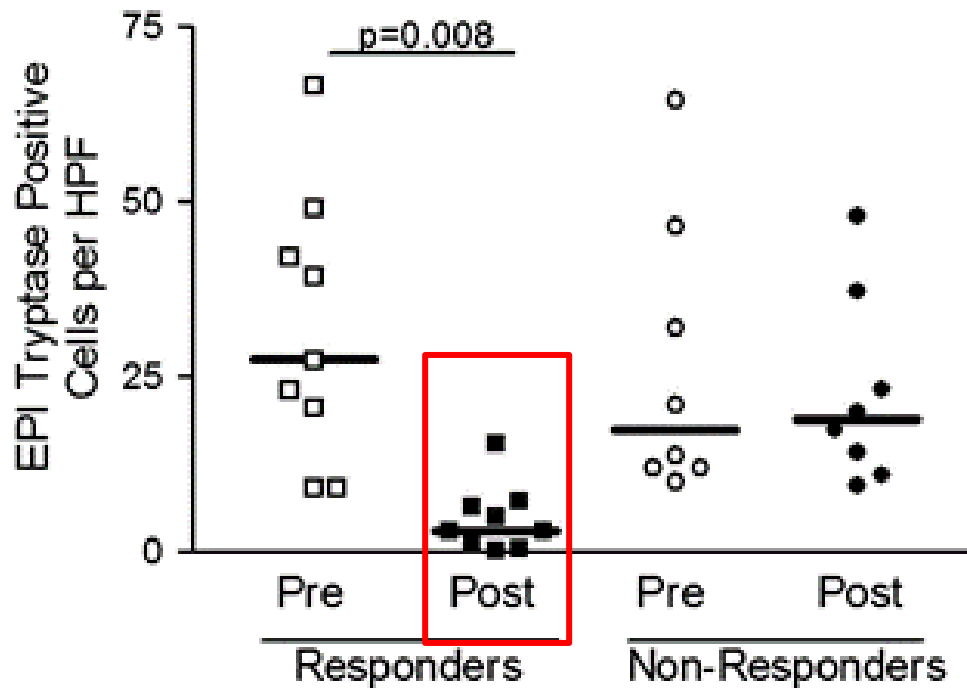
Activated mast cells are increased in EoE and differentiate from other types of esophagitis



Mast cell density decreases with therapy

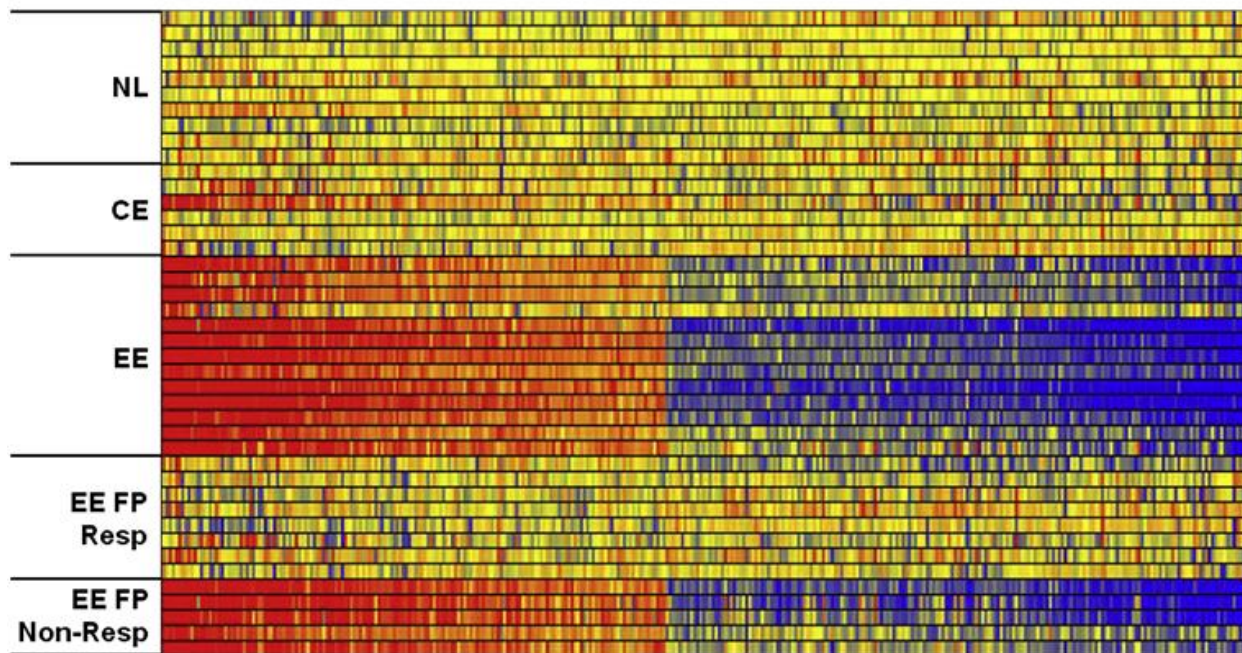


Mast cell density decreases with therapy





Mast cell transcriptome in EoE normalizes with swallowed steroids





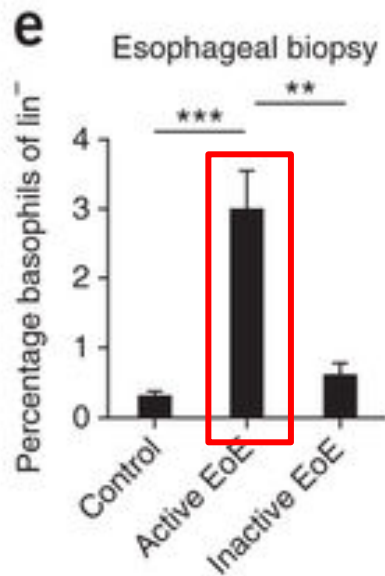
➤ Clin Gastroenterol Hepatol. 2021 Oct;19(10):2102-2111. doi: 10.1016/j.cgh.2020.08.013.
Epub 2020 Aug 12.

Mast Cell and Eosinophil Counts in Gastric and Duodenal Biopsy Specimens From Patients With and Without Eosinophilic Gastroenteritis

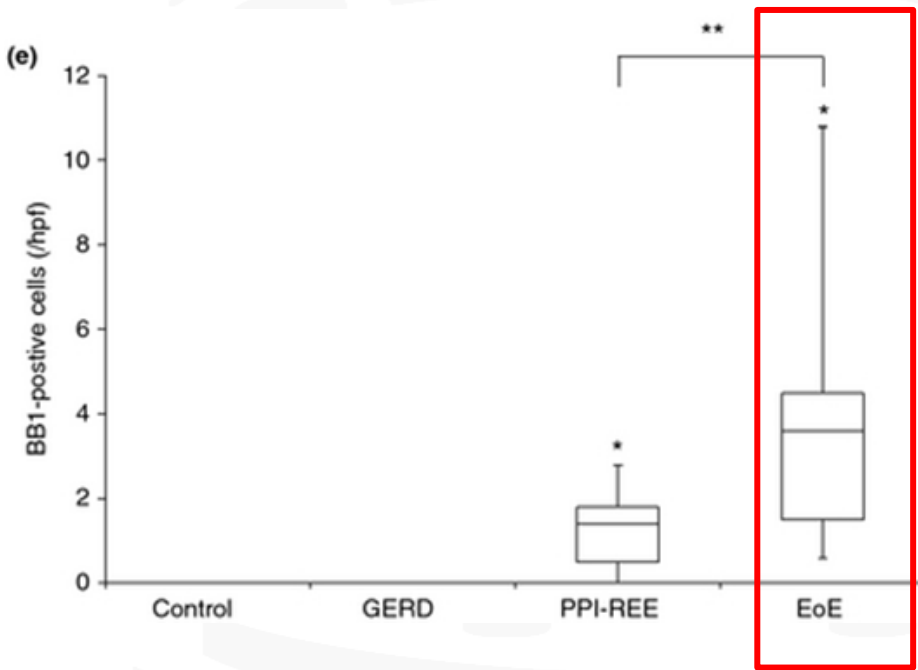
Craig C Reed¹, Robert M Genta², Bradford A Youngblood³, Joshua B Wechsler⁴,
Evan S Dellon⁵

- Gastric and duodenal biopsy specimens from patients with EGIDs had significant increases in mean mast cell counts
- There was a correlation between mean mast cell and eosinophil counts in duodenal biopsy specimens ($R = 0.47$; $P = .01$)
- The mean mast cell and eosinophil counts did not correlate with symptoms or endoscopic features of EGIDs

Elevated basophils in EoE



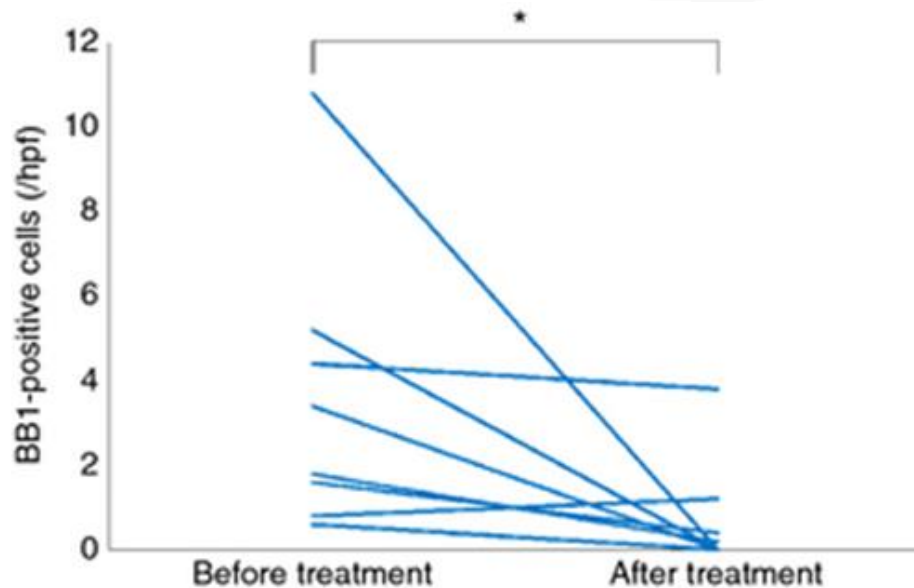
Noti M et al Nature Med 2013



*Iwakura et al Aliment Pharm
Therap 2015*



Basophil density is reduced in response to therapy

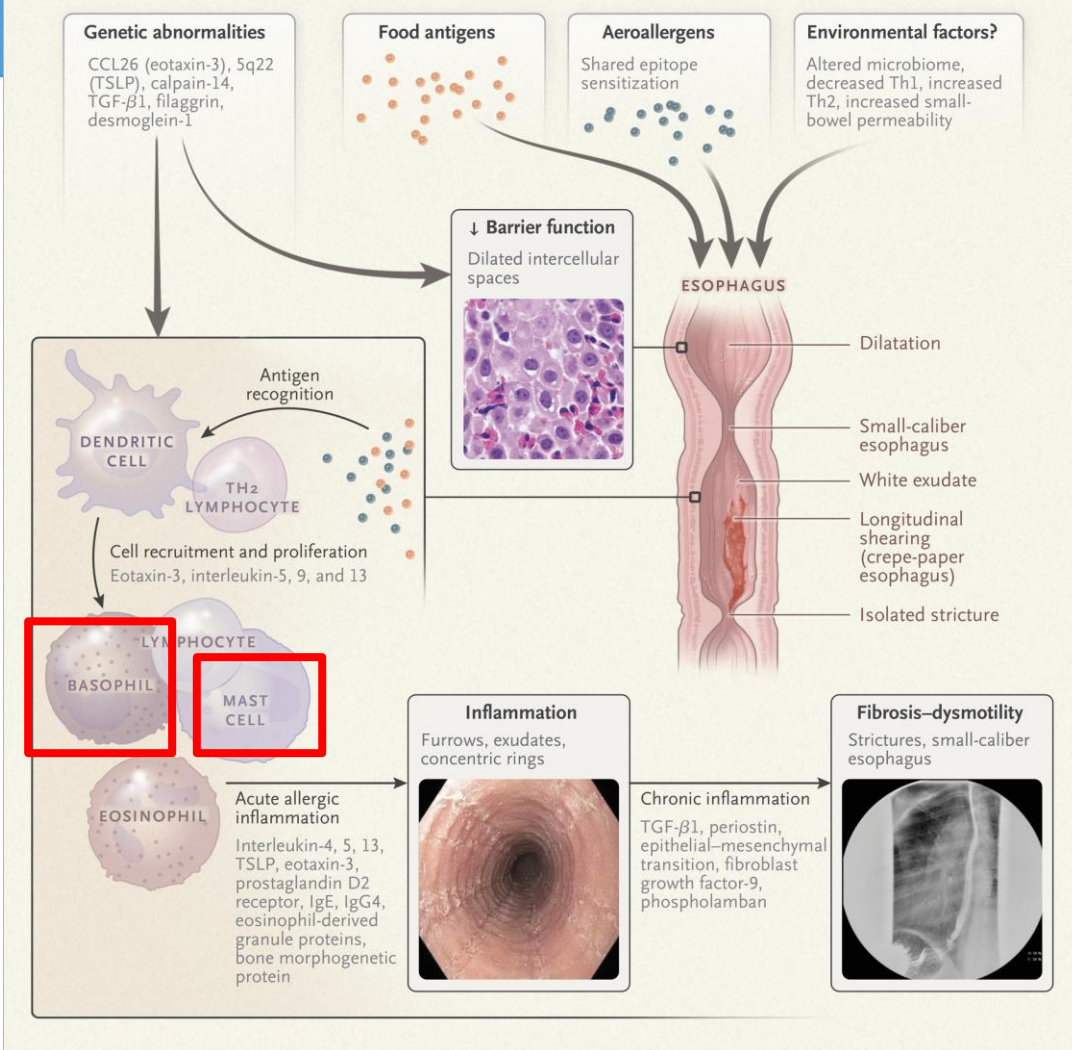


Iwakura et al Aliment Pharm Therap 2015

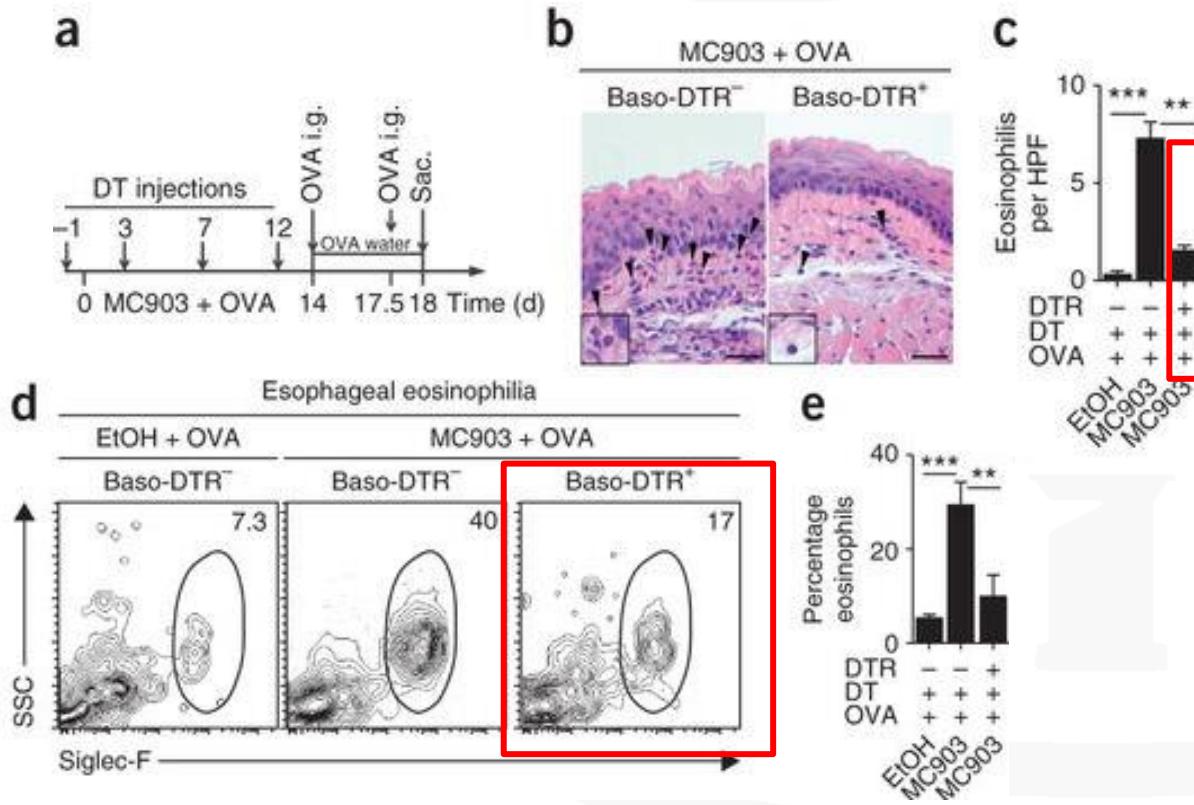


Mast cells and basophils are key components of the inflammatory milieu in EoE and respond to therapy

*Furuta & Katzka,
NEJM 2015*



Basophil deficiency limits EoE-like disease in mice





**If allergy is important in EoE,
what is the best approach for
testing and treatment?**



My approach to allergy testing in EoE

Children

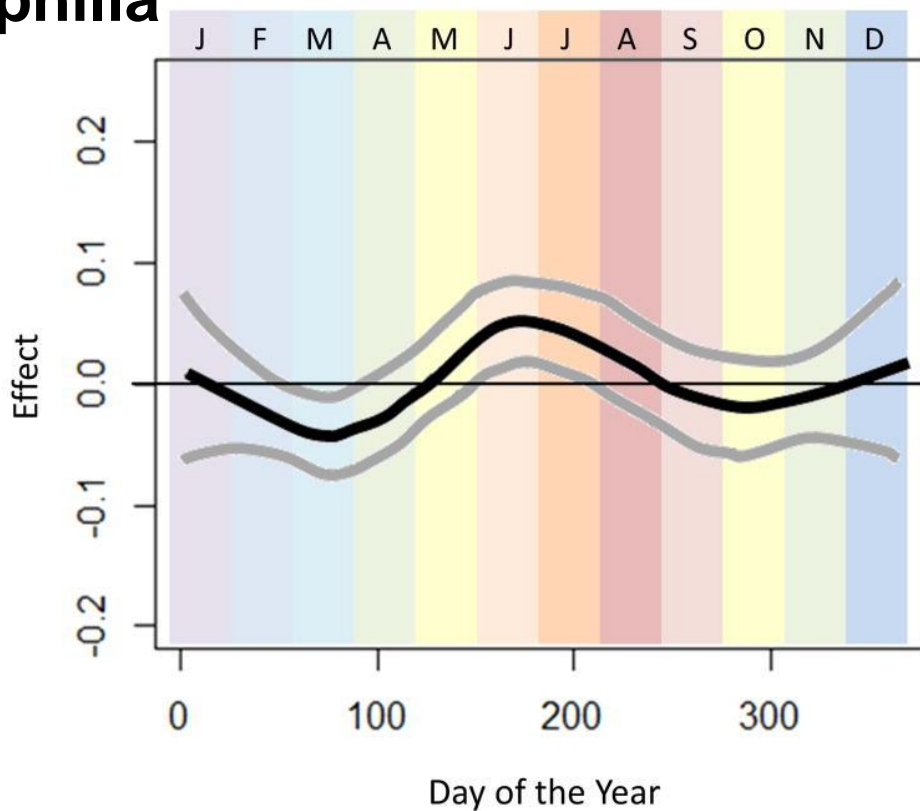
- **Food: serum testing allows quantitation but many kids prefer SPT to blood draw**
- **Consider empiric elimination diet**

Teens / Adults (they are gonna do what they want)

- **Food: Empiric vs Targeted based on serum testing ("for the patient")**
- **Environmental: prefer SPT**



Seasonal variation of esophageal eosinophilia





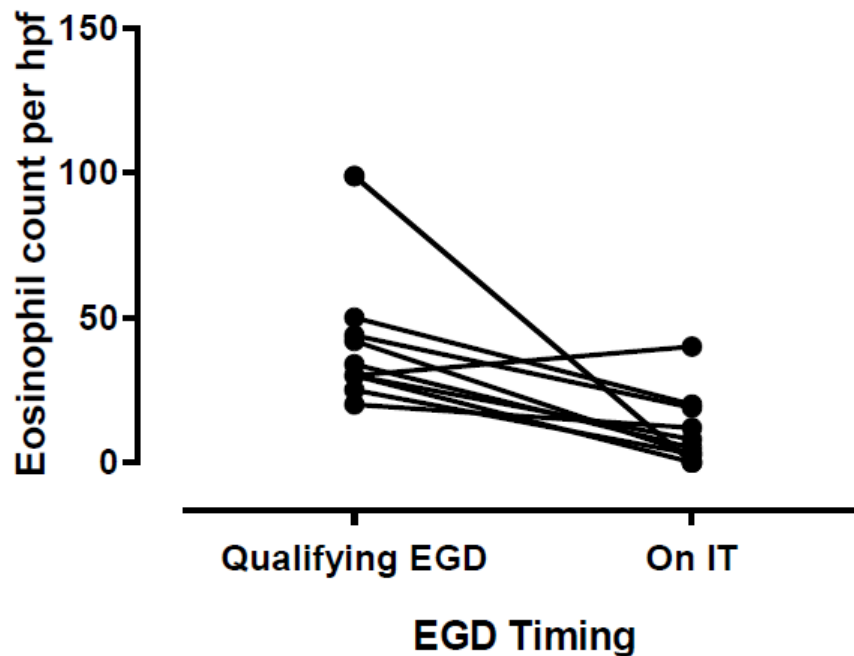
Will EoE respond to SCIT?

AGE	IT START DATE	IT STOP DATE	Allergens in IT	EOE DX BEFORE IT TX
22	7/9/2012	continues	DM, cat, dog, tree, grass weed	Diagnosed with EoE on 11/2/2009
46	2/20/2013	continues	DM, CR, cat, tree, grass, weed	Diagnosed with EoE on 08/4/2004
62	10/17/2011	8/20/2016	DM, tree, grass, weed	Diagnosed with EoE on 6/19/2006
45	10/15/2013	continues	DM, mold, CR, weed	
17	11/13/2014	continues	DM, cat, mold, tree, grass, weed	Diagnosed with EoE on 7/15/2011
14	4/25/2011	6/24/2013	DM, cat, dog, tree, grass, weed	Diagnosed with EoE on 3/3/2014
27	4/23/2014	continues	Ragweed, mold	Diagnosed with EoE on 12/15/2008
45	10/2/2012	8/10/2015	DM, cat, dog, tree, grass, weed	Diagnosed with EoE on 1/28/2009
35	7/13/2016	continues	Dog, grass, mold	Diagnosed with EoE in 2005
55	8/10/2010	9/18/2012	Cat, weed, mold	Diagnosed with EoE in 2008
24	12/21/2015	continues	DM, grass	Diagnosed with EoE on 9/4/2014
38	5/7/2016	continues	Cat, dog, grass, tree	Diagnosed with EoE on 11/14/2015



Will EoE respond to SCIT?

EoE and IT
UNC retrospective review





Conclusions

- **EoE is an complex clinicopathologic disorder that has allergic underpinnings but the best testing is debatable**
- **Definition in evolution...as is natural history, therapy, monitoring**

References

- Furuta GT & Katzka DA. Eosinophilic Esophagitis. *N Engl J Med*. 2015 Oct 22; 373: 1640–1648.
- Not M, et al. TSLP-elicited basophil responses can mediate the pathogenesis of eosinophilic esophagitis. *Nat Med*. 2013 Aug; 19: 1005–1013.
- Aceves SS, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy*. 2010 Jan; 65: 109–116.
- Green DJ, et al. The Role of Environmental Exposures in the Etiology of Eosinophilic Esophagitis: A Systematic Review. *Mayo Clin Proc*. 2015;90(10):1400–1410.
- Cox L, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127:S1–55.
- Ramirez RM, Jacobs RL. Eosinophilic esophagitis treated with immunotherapy to dust mites. *J Allergy Clin Immunol*. 2013;132(2):503–504.
- Robey BS, et al. Subcutaneous immunotherapy in patients with eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2019;122(5):532–533 e533.
- Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J Allergy Clin Immunol*. 2017;140(6):1485–1498.
- De Swert L, et al. Eosinophilic gastrointestinal disease suggestive of pathogenesis-related class 10 (PR-10) protein allergy resolved after immunotherapy. *J Allergy Clin Immunol*. 2013;131(2):600–602 e601–603.
- Calderon MA. Could Allergen Immunotherapy be a Therapeutic Intervention in Eosinophilic Oesophagitis? *J Allergy Clin Immunol*. 2016;137:AB98.
- Castilano A, Zacharias D. Immunotherapy as Treatment for Aeroallergen Triggered Eosinophilic Esophagitis. *Ann Allergy Asthma Immunol*. 2013;111:A62.
- Wells R, Fox AT, Furman M. Recurrence of eosinophilic oesophagitis with subcutaneous grass pollen immunotherapy. *BMJ Case Rep*. 2018;2018



