Eosinophilic Esophagitis (EoE): Lessons Learned from Medicaid and the UVA EoE Cohort

Emily C. McGowan, MD PhD
Associate Professor, Division of Allergy & Immunology
61st Annual Swineford Allergy Conference
April 15, 2023

Disclosures

- Received funding from the NIH/NIAID, AAAAI/FARE, and American College of Gastroenterology
- Received research funding from Regeneron (to UVA)

Objectives

- Provide a brief clinical overview of eosinophilic esophagitis
- Discuss recent findings on the epidemiology of EoE in the U.S. Medicaid population
- Review the known pathophysiology of EoE and discuss and the potential role of IgG4

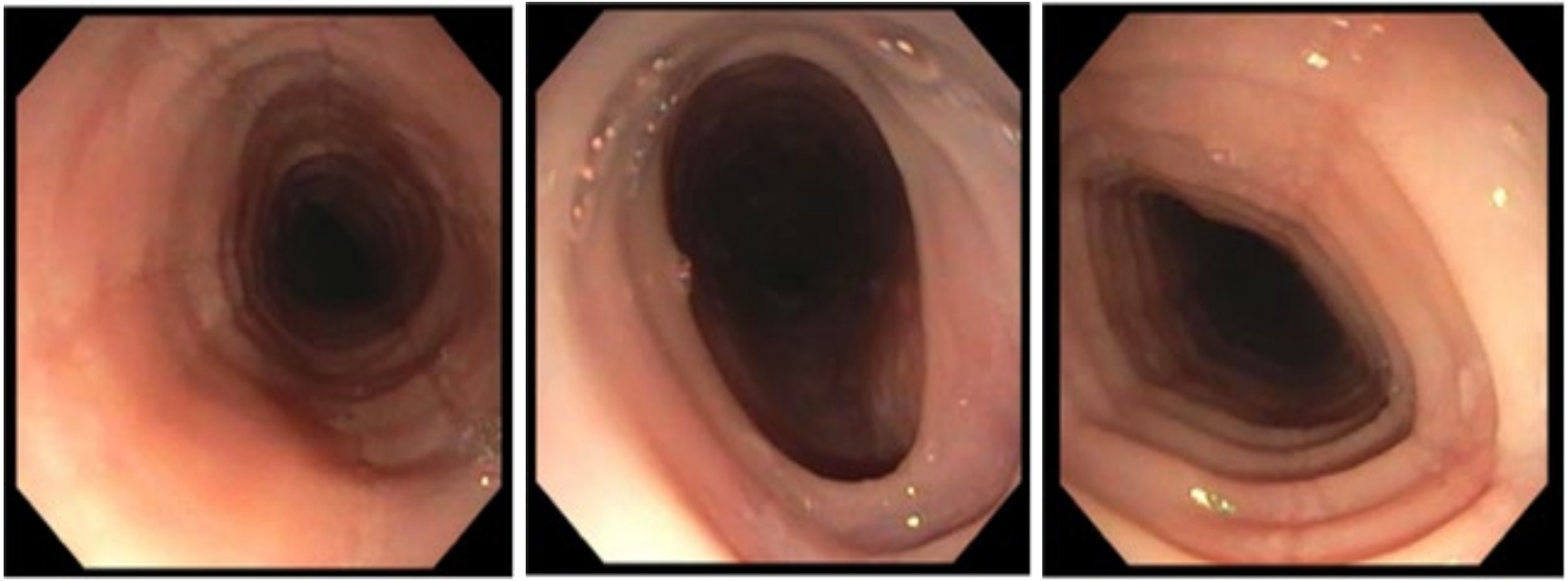
Case Presentation

- 34 year-old Caucasian man presents to the allergy clinic for evaluation of allergic rhinitis
  - Itchy eyes and sneezing in the spring/fall
  - He endorses itching in his mouth when eating almonds, hazelnuts, and some raw fruits
  - Skin prick testing is markedly positive to trees, grasses, and weeds

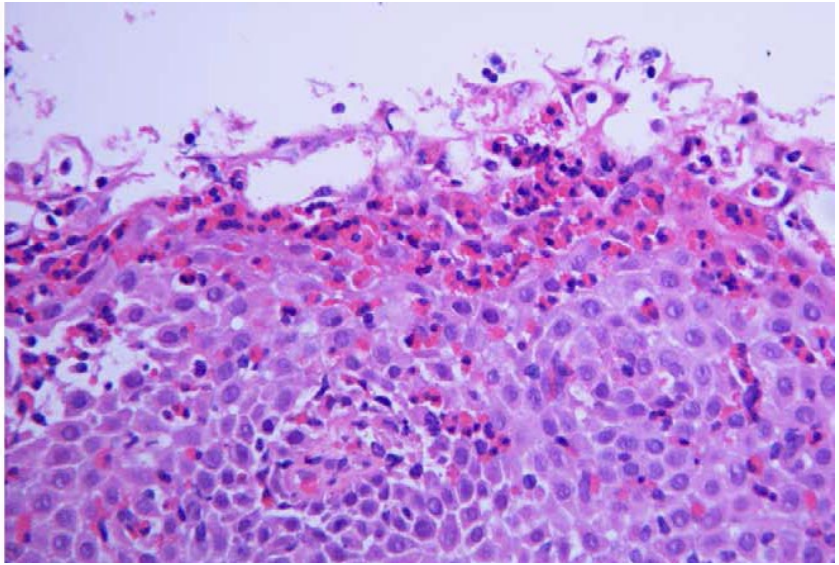
Case Presentation (continued)

- On review of systems, he endorses dysphagia
  - Present since he was 12
  - His brothers always made fun of him because he was a slow eater and choked frequently
  - He can’t eat without drinking water
  - His symptoms are worse when eating chicken and beef

Upper Endoscopy



Pathology



- *Distal:* > 25 eosinophils/hpf
- *Middle:* > 25 eosinophils/hpf
- *Proximal:* > 25 eosinophils/hpf

- Subepithelial fibrosis present

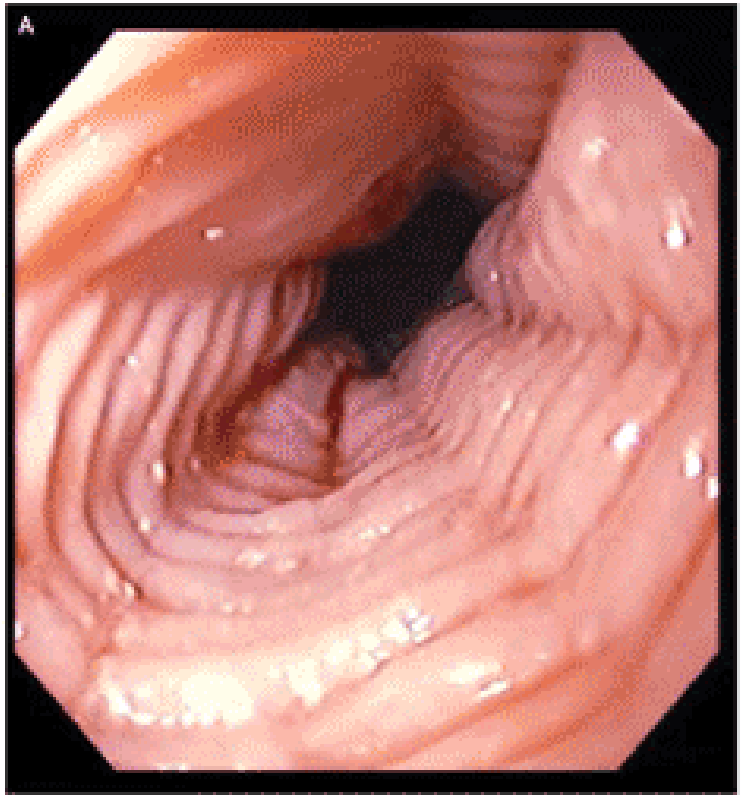
Other potential causes of esophageal eosinophilia were excluded

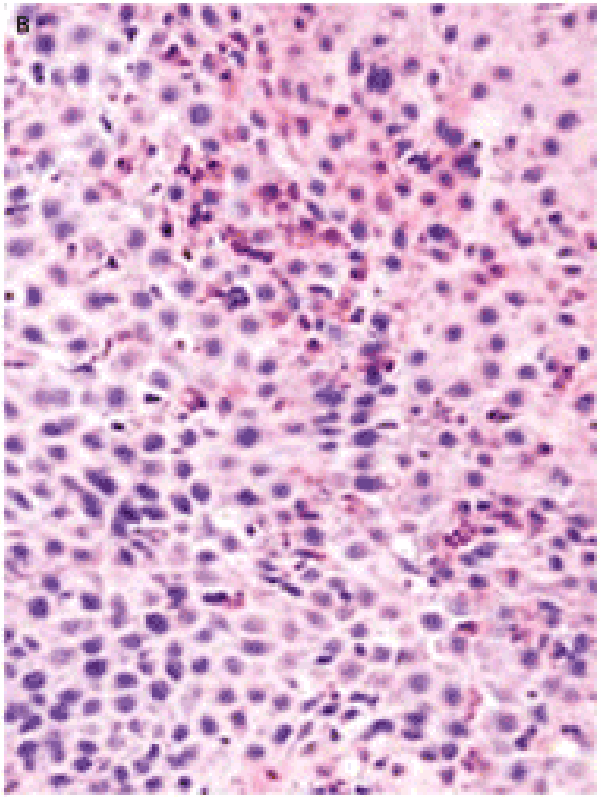
Definition of EoE (2018)

- **A clinicopathologic disorder defined by the following criteria:**
  - Symptoms related to esophageal dysfunction
  - Eosinophil-predominant inflammation on esophageal biopsy (≥15 eos/hpf)
  - Secondary causes of esophageal eosinophilia are excluded

Dellon ES *et al*. Gastroenterology 2018

Eosinophilic Esophagitis





Project #1:

Epidemiology of EoE

Epidemiology

- Males > Females (~3:1)
- Caucasians > other race/ethnicities
- Has been reported in every continent
- Strongly associated with atopic diseases
- Can run in families
  - Brother with EoE: RR 64
  - Father with EoE: RR 43
- Possible seasonal variation

Dellon ES, *Gastroenterology,* 2018
Rothenberg ME *et al*, Gastroenterology 2015

Prevalence Estimates

- Prevalence estimates are highest in the United States, Western Europe, and Australia

- **Prevalence estimates:**
  - General population: 22-90/100,000
  - Among those with food allergy: ~5%
  - Among those undergoing EGD for dysphagia: 12-23%
  - Among those undergoing EGD for food impaction: 46-63%

Dellon ES, Gastroenterology, 2018
Arias A *et al*, AP&T, 2016
Hill DA *et al*, JACI-IP, 2017
Prasad GA *et al*, Am J Gastro, 2007
Hiremath GS *et al, Dig Dis Sci, 2015*

Knowledge Gaps

- Disparities exist in asthma morbidity and food allergy diagnosis among impoverished children
- Our understanding of the association between poverty, urbanization, and EoE is poor
- Previous studies estimating the prevalence of EoE using administrative data have not included the U.S Medicaid population

Keet CA JACI 2017; McGowan EC Annals 2015

Questions

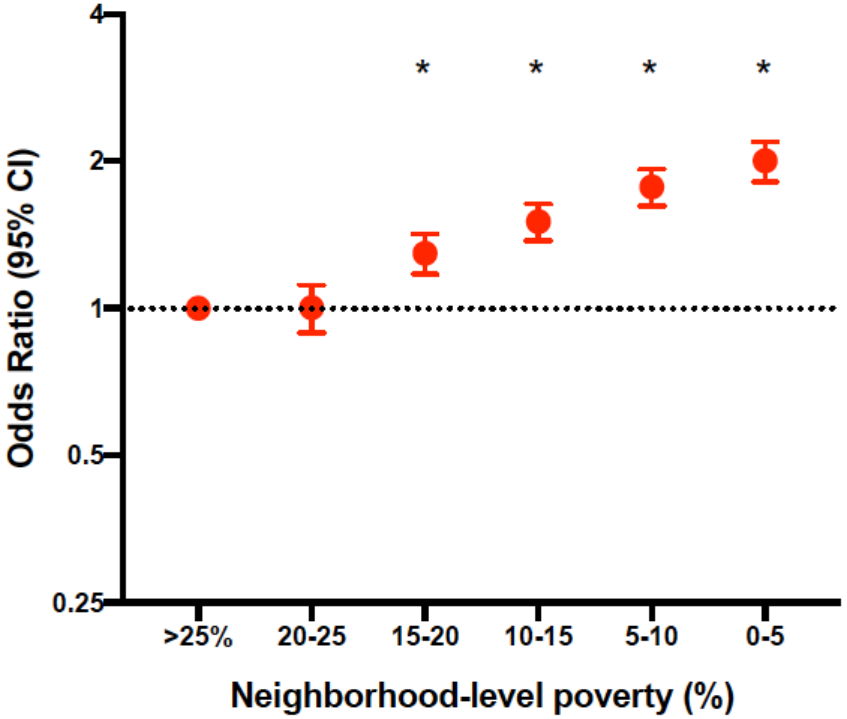
- What is the prevalence of EoE in the U.S. Medicaid population?
- Is there any association between EoE, poverty, and urbanization?

EoE Prevalence in Medicaid

	Overall Medicaid Population	EOE Cases	EOE Prevalence (per 100,000)
Overall	19,325,650	4,974	25.74
Gender			
Male	9,745,097 (50%)	3,459	35.49
Female	9,580,553 (50%)	1,515	15.81
ZCTA-Level Poverty			
0-5%	2,027,395 (10%)	861	42.47
5-10%	4,242,416 (22%)	1,496	35.26
10-15%	4,427,585 (23%)	1,213	27.40
15-20%	3,293,319 (17%)	669	20.31
20-25%	2,068,216 (11%)	291	14.07
25-100%	3,266,719 (17%)	444	13.59

McGowan EC *et al, JACI IP* 2020

Inverse Association with Poverty



- Higher neighborhood-level poverty (>20%) is protective for EoE diagnosis
- This is true despite taking into account sex, age, race/ethnicity, state, and urbanization

McGowan EC *et al, JACI IP* 2020

Associations with Race, Urbanization

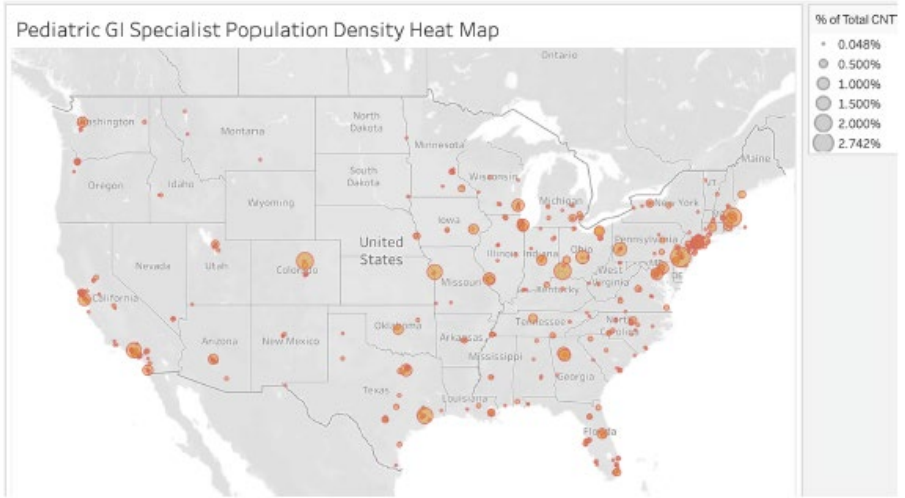
	Adjusted OR	p value
Race/Ethnicity		
White	REF	
Black	0.41 (0.37 – 0.44)	<0.001
Asian	0.37 (0.28 – 0.48)	<0.001
Hispanic	0.31 (0.27 – 0.35)	<0.001
Other	0.39 (0.34 – 0.44)	<0.001
Unknown	1.60 (1.45 – 1.76)	<0.001
Urban/Rural Status		
Large Central Metro	REF	
Large Fringe Metro	0.94 (0.86 – 1.03)	0.19
Medium Metro	0.95 (0.86 – 1.04)	0.28
Small Metro	0.78 (0.69 – 0.88)	<0.001
Micropolitan	0.78 (0.70 – 0.88)	<0.001
Noncore (rural)	0.68 (0.59 – 0.78)	<0.001

McGowan EC *et al, JACI IP* 2020

Then . . .

Do rural health disparities affect prevalence data in pediatric eosinophilic esophagitis?

Cameron Sabet[a]
Amy D. Klion, MD[b]
Dominique Bailey, MD[c]
Elizabeth Jensen, MPH, PhD[d]
Mirna Chehade, MPH, PhD[e]
J. Pablo Abonia, MD[f]
Marc E. Rothenberg, MD, PhD[f]
Glenn T. Furuta, MD[g,h]
Amanda B. Muir, MD, MSTR[a]
CEGIR Investigator Group

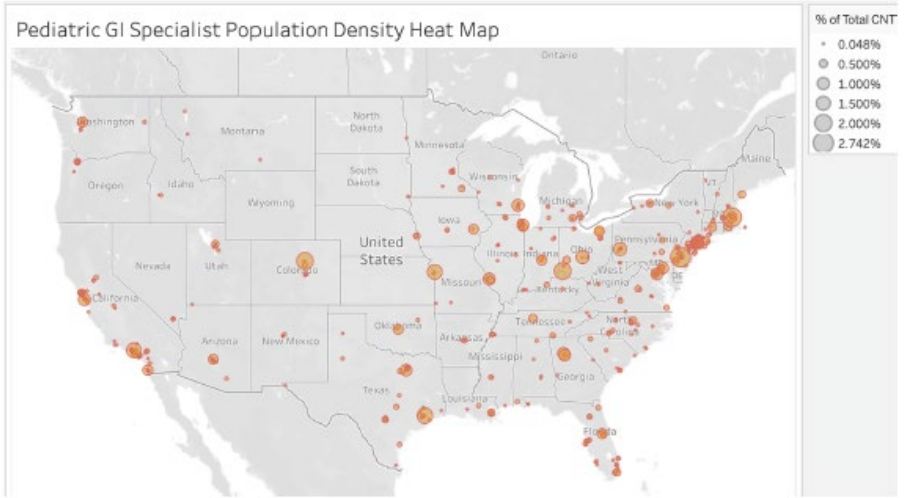


Sabet C *et al,* JACI-IP 2021

Then . . .

Reply to "Do rural health disparities affect prevalence data in pediatric eosinophilic esophagitis?"

Emily C. McGowan, MD, PhD[a,b]
Joshua P. Keller, PhD[c]
Evan S. Dellon, MD, MPH[d]
Roger Peng, PhD[e]
Corinne A. Keet, MD, PhD[f]

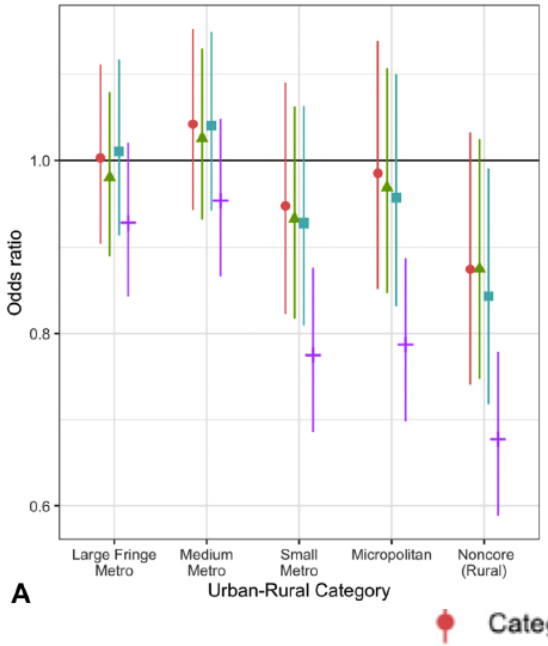


Yes – We 100% agree.

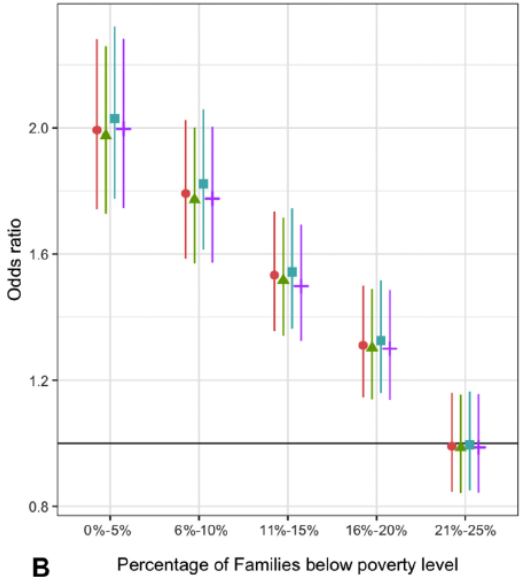
McGowan EC *et al,* JACI-IP 2021

Disparities Exist in EoE Diagnosis

Urban-Rural



Poverty



Categorical Linear Log-Linear None

McGowan EC *et al,* JACI-IP 2021

Lesson #1

- The “protective” effect of living in a rural environment was explained by distance to a pediatric provider (i.e. underdiagnosis)
- The protective effect of poverty did not change
  - Protective environmental exposures?
  - Decreased access to specialty care?
  - Inability to take off work for appointments?
  - Distrust in medical providers?

Is this just the tip of the iceberg?

The diagnosis requires an endoscopy

Lack of access to specialty providers

Other financial barriers to care

Symptoms are gradually progressive

Patients modify eating behaviors

We rarely ask questions about dysphagia

Questions

- What is the prevalence of EoE symptoms in an allergy clinic population?
- Do any of those patients have undiagnosed EoE?

Pilot Study

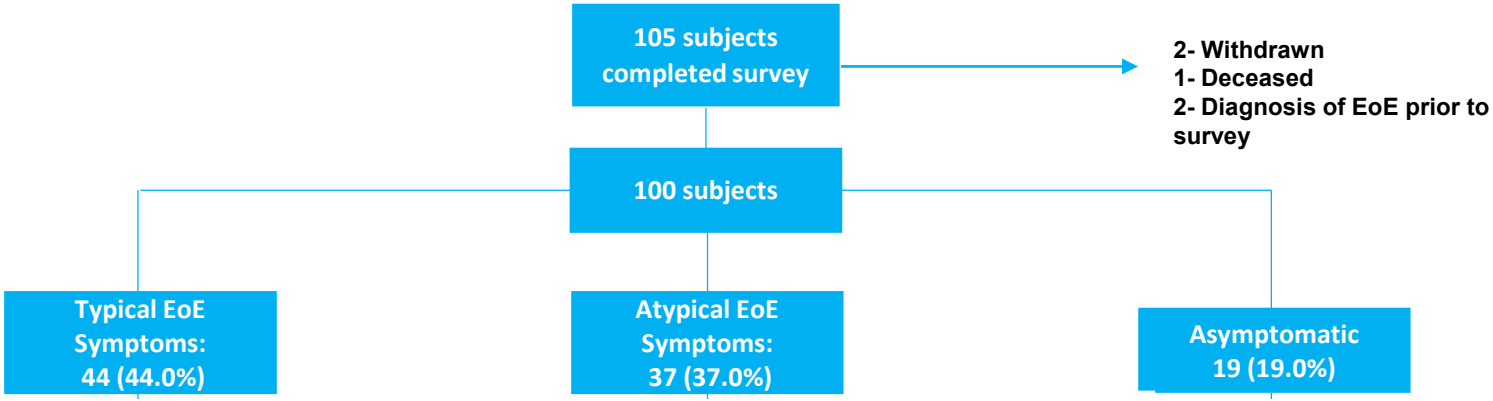
1. **Allergy Clinic Patients**
   - Asthma
   - Allergic Rhinitis
   - IgE-Mediated Food Allergy
   - Eczema

2. **Unselected Adults**

	Atopics n=101	Control N=102	P-value
Trouble eating solid food			
Once or more in the last 14 days	27 (26.7%)	2 (2.0%)	**p=<0.001**
Rarely/ Never	71 (71.0%)	100 (98.0%)	
Coughing or choking while swallowing food			
Once or more in the last 14 days	42 (41.6%)	2 (2.0%)	**p=<0.001**
Rarely/ Never	57 (56.4%)	100 (98%)	
Pain/Discomfort with eating solid food			
Once of more in the last 14 days	33 (32.7%)	4 (3.9%)	**p=<0.001**
Rarely/Never	60 (65.2%)	98 (96.1%)	
In the last 12 months....Had Food stuck in your throat for 30 min.			
Once	3 (3%)	0 (0.0%)	
Twice	4 (4%)	0 (0.0%)	**p=<0.001**
More than Twice	5 (5%)	0 (0.0%)	

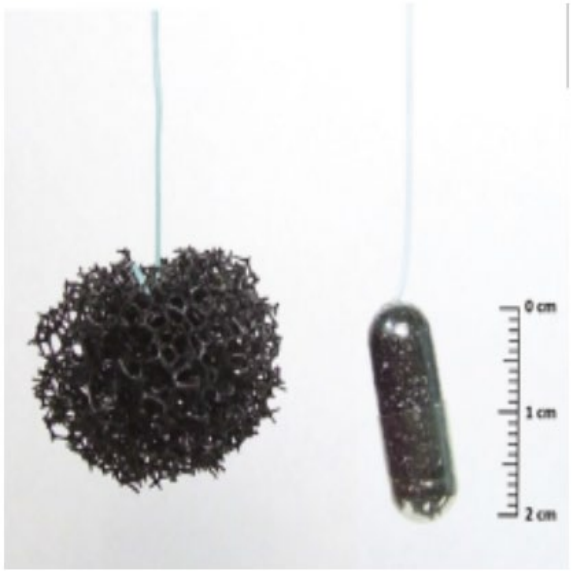
Both groups completed the Brief Esophageal Dysphagia Questionnaire

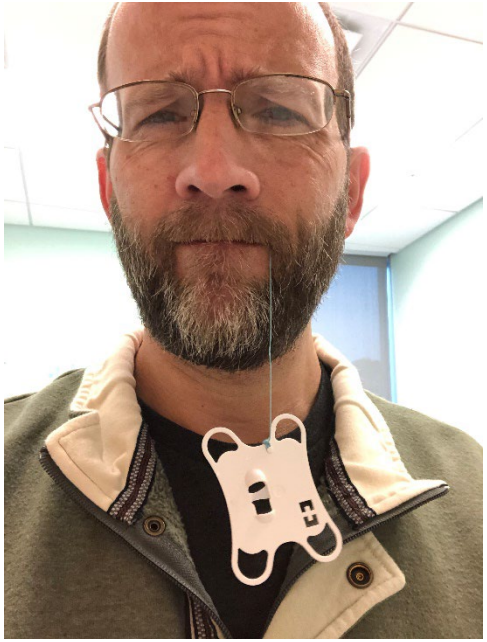
Eid R *et al,* JACI-IP 2022



Eid R *et al,* JACI-IP 2022

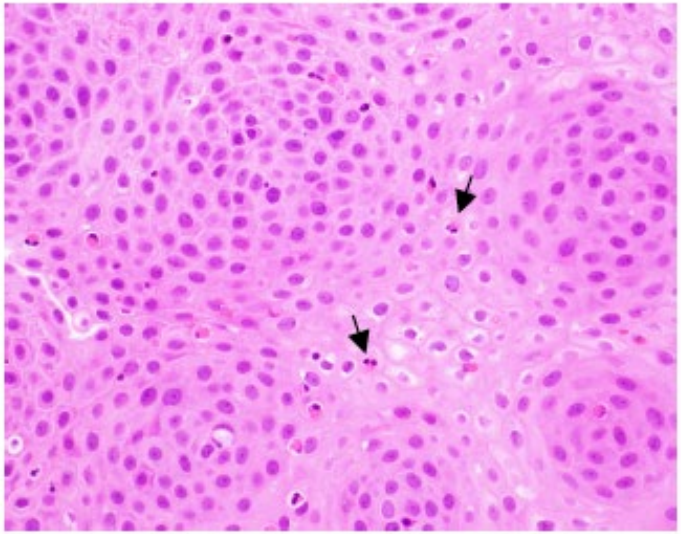
The Cytosponge





Eosinophils via the Cytosponge

A. Biopsy histology



B. Cytosponge cytology

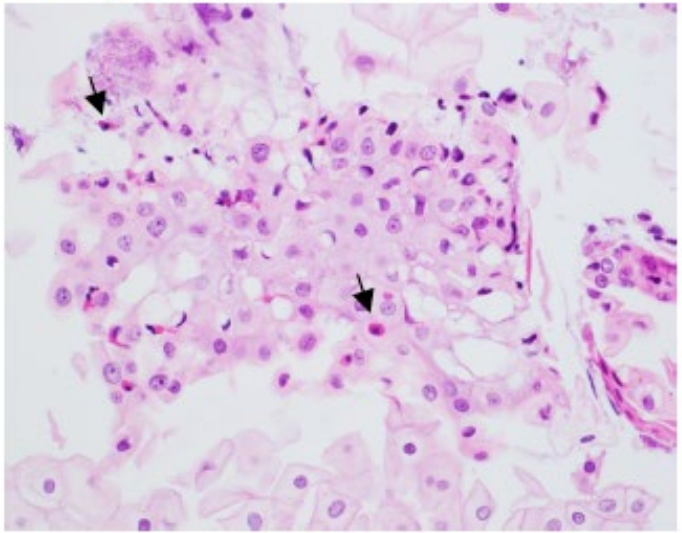
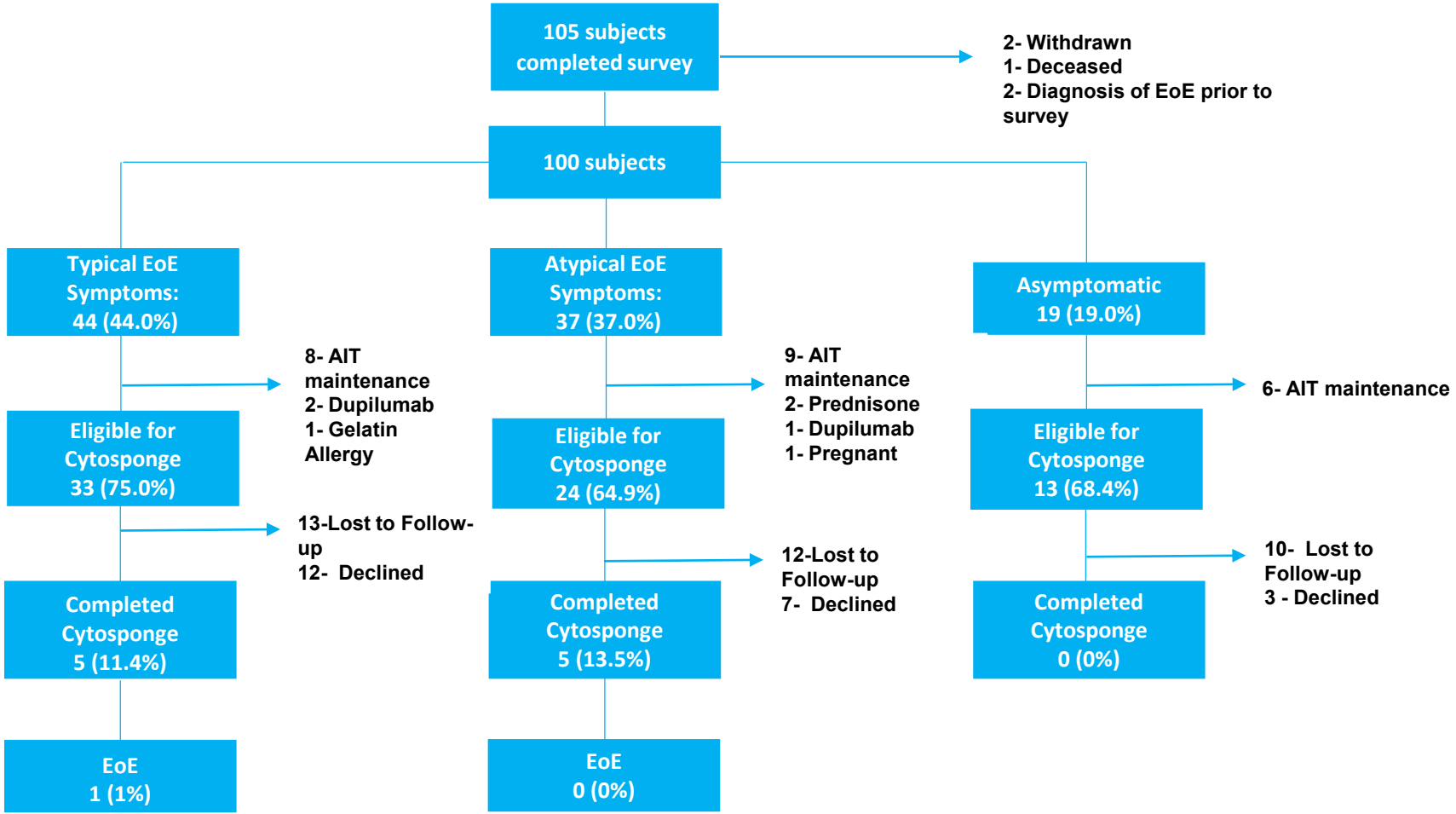
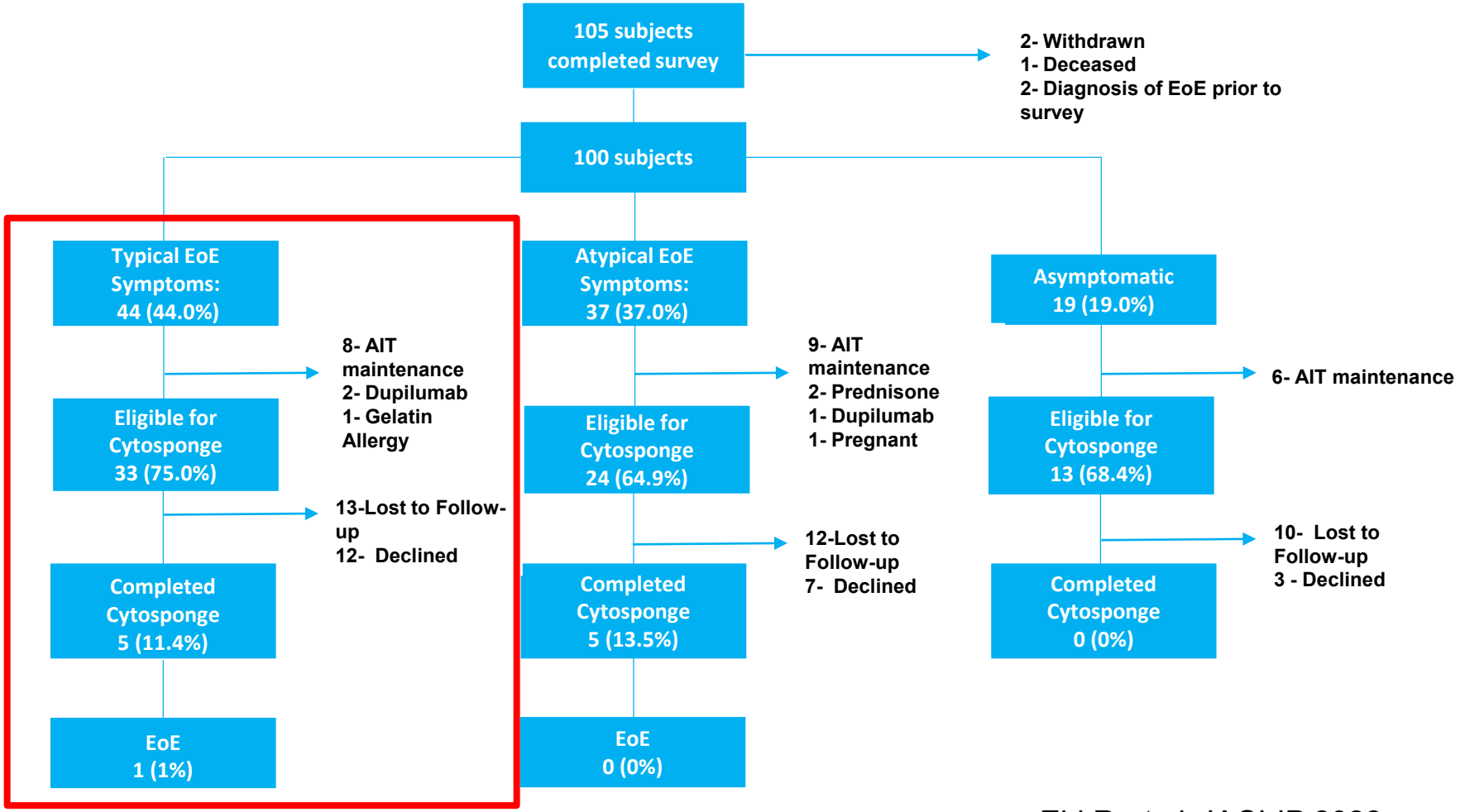


Figure 1: Histology obtained via esophageal biopsy and Cytology obtained via the Cytosponge in the same individual with EoE. Arrows represent eosinophils.

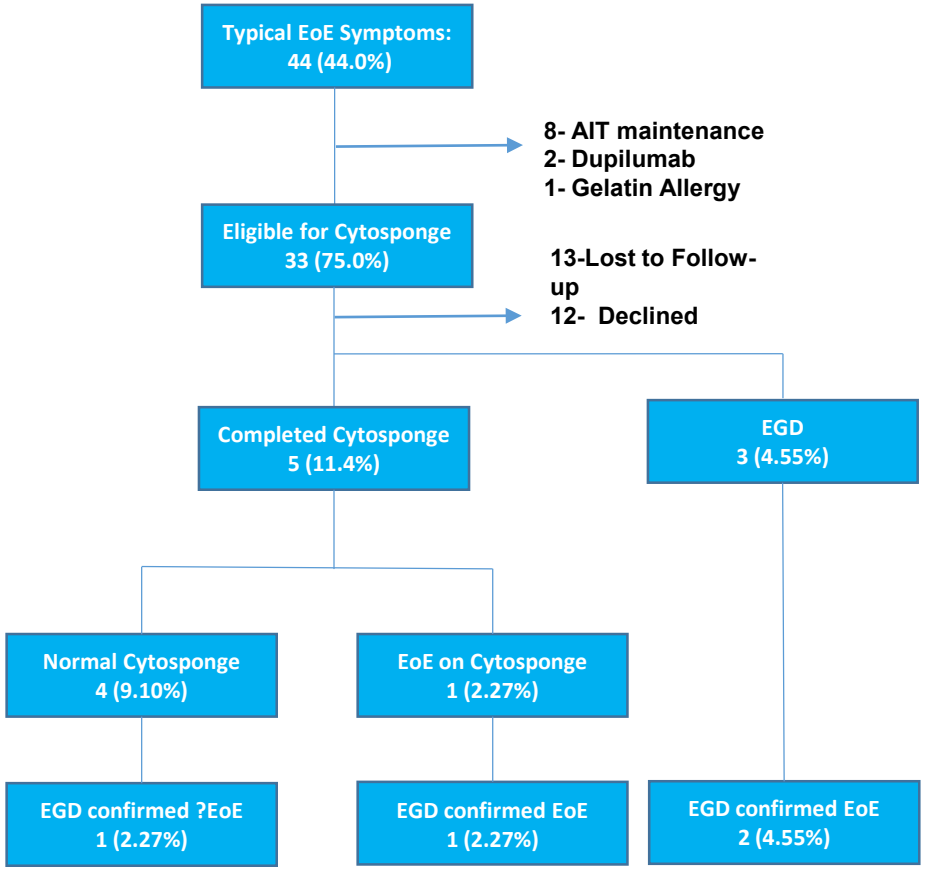
McGowan EC, unpublished data



Eid R *et al,* JACI-IP 2022



Eid R *et al*, JACI-IP 2022



Weighted estimate of EoE: 8.8 – 16.5% of allergy patients

Eid R *et al,* JACI-IP 2022

Lesson #2

- The prevalence of EoE symptoms in allergy patients is very high
- There is likely undiagnosed EoE in patients with other allergic conditions
- As allergists, we should always ask about symptoms of dysphagia in our allergy patients

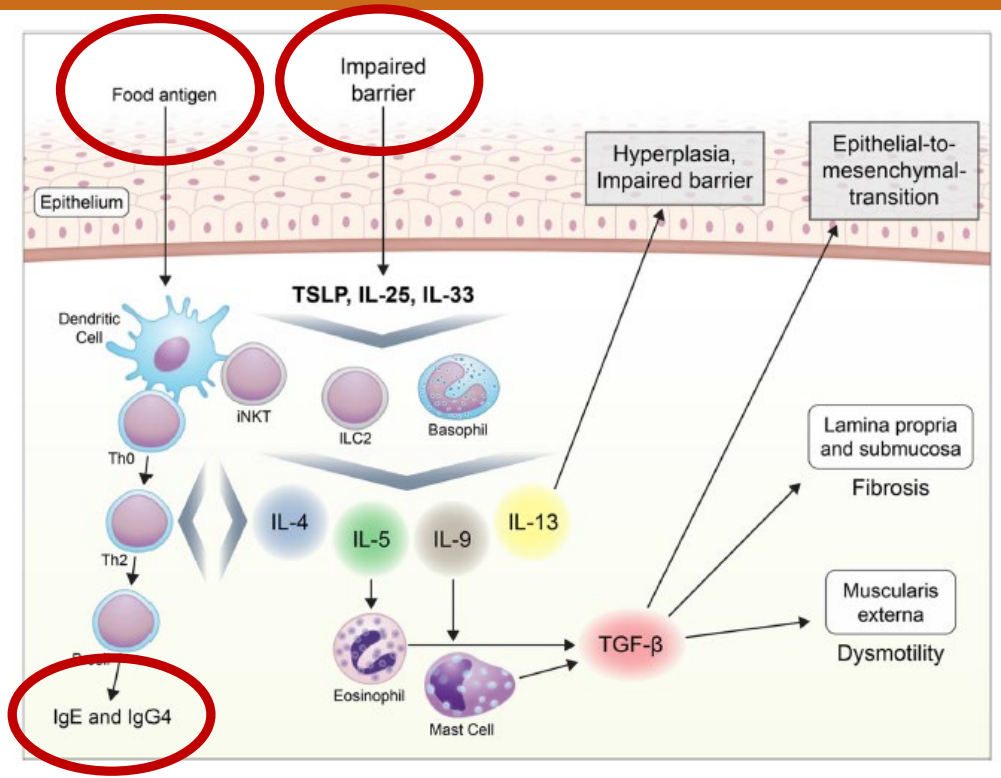
Project #2:

EoE and the Enigma of IgG4

Knowledge Gap

- EoE is driven by food antigens (milk, wheat, egg, soy, etc)
- The mechanisms underlying this food-induced inflammation remain unknown
- Because of this knowledge gap, we do not have accurate diagnostic tests to identify food triggers

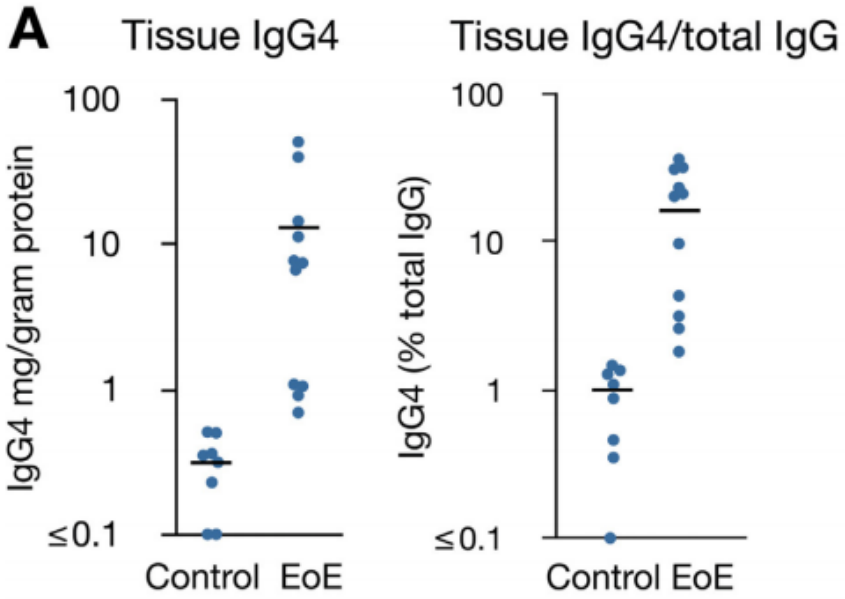
Pathophysiology



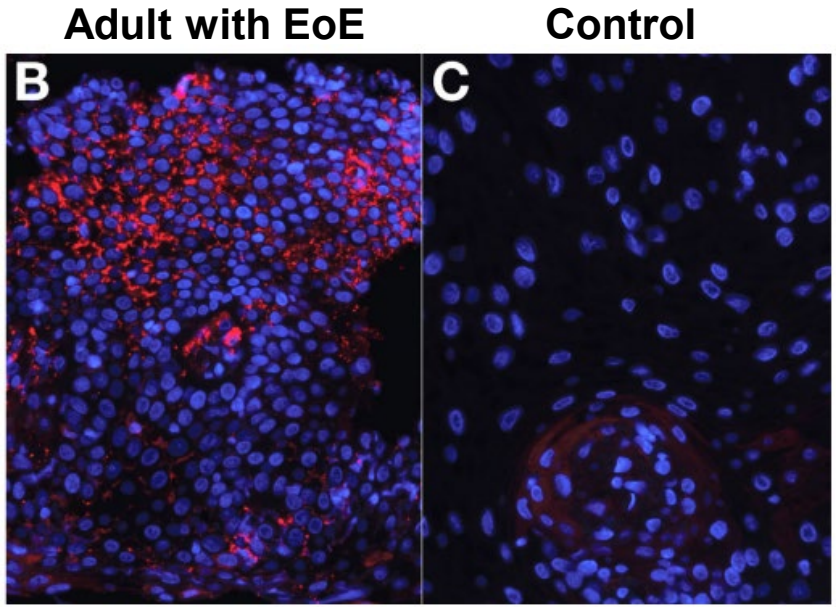
Davis BP, *Clin Rev Allergy and Immunol*, 2018

CLINICAL—ALIMENTARY TRACT

Eosinophilic Esophagitis in Adults Is Associated With IgG4 and Not Mediated by IgE



IgG4 content of esophageal tissue homogenate in adults with EoE compared with control subjects



Red = granular intercellular IgG4
Blue = DAPI nuclear counterstain
Co-staining for complement 9 (Green) is negative

Clayton F, Gleich GJ, Peterson KA *et al*, *Gastroenterology*, 2014

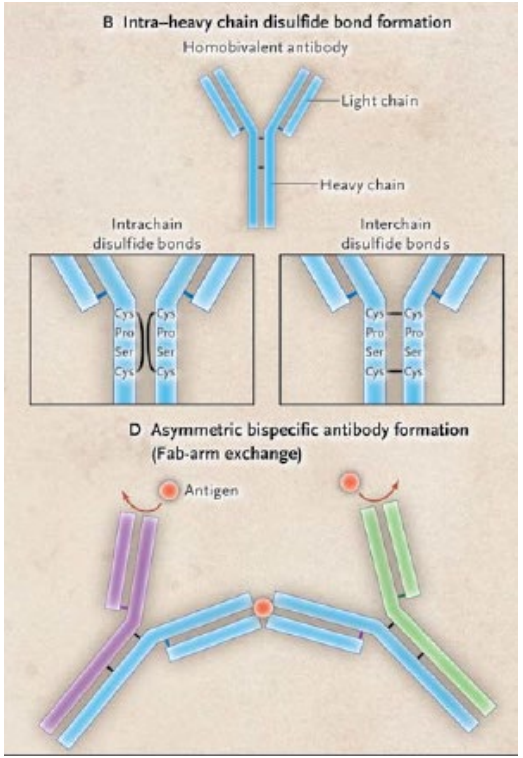
Subsequent Studies

- Granular deposits of IgG4 and IgG4-containing plasma cells have been found in the esophagi of patients with EoE
- Intrasquamous IgG4 deposits can distinguish EoE from GERD
- Total IgG4 and food-specific esophageal IgG4 levels decrease in patients who respond to diet
- Esophageal IgG4 levels correlate with esophageal eosinophil counts, histologic grade, stage scores, and cytokine expression in children with EoE

Clayton *et al,* 2014; Zuckerberg *et al,* 2015; Wright *et al,* 2016; Mohammad *et al,* 2018; Rosenberg *et al,* 2018

Overview of IgG4

- Least abundant IgG subclass
- Increases in response to IL-4 and IL-13, as well as IL-10, and IL-21
- Flexible hinge region allows Fab arm exchange
- Limited ability to form immune complexes
- Pathologic in certain diseases

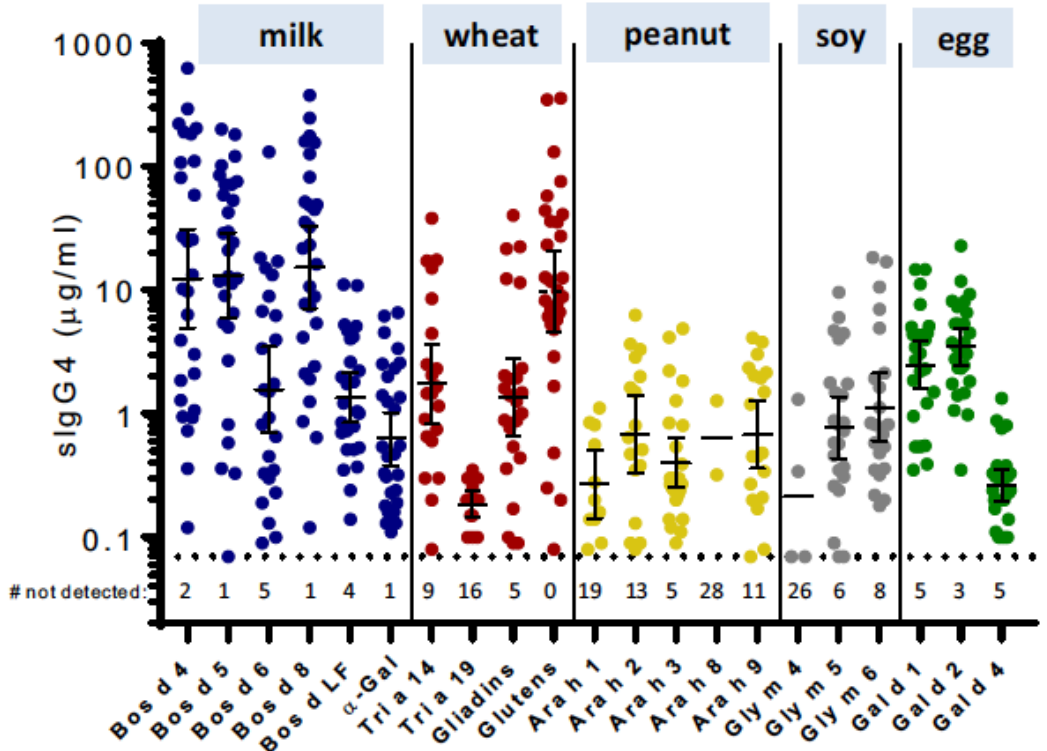


Stone *et al*, NEJM, 2012

Question

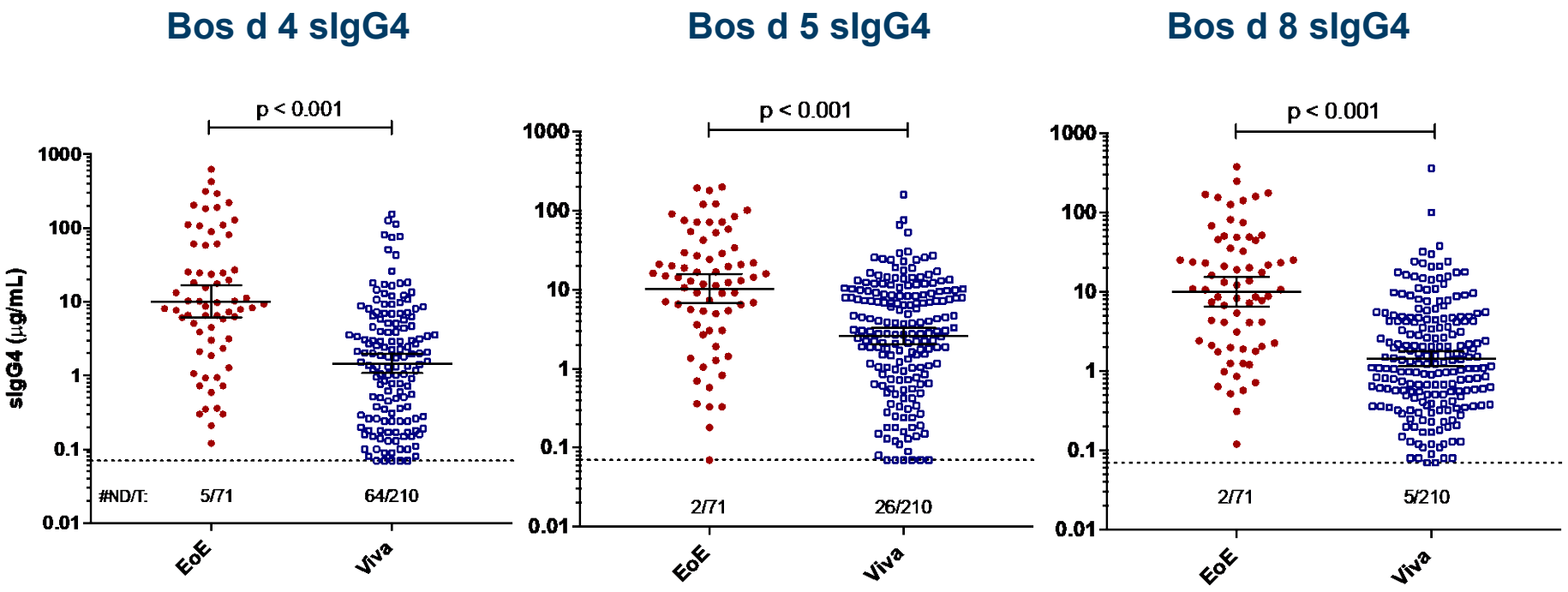
- Are food-specific IgG4 levels higher in children with EoE than unselected controls?

Elevated sIgG4 to Milk and Gluten



Schuyler A, McGowan EC *et al*, *JACI, 2018*

sIgG4 to Milk Proteins are Elevated in EoE



Schuyler A, McGowan EC *et al*, *JACI, 2018*

Question

- Are serum food-specific IgG4 levels higher in patients with EoE than controls with a **matched distribution of allergic disease**?

UVA EoE Cohort

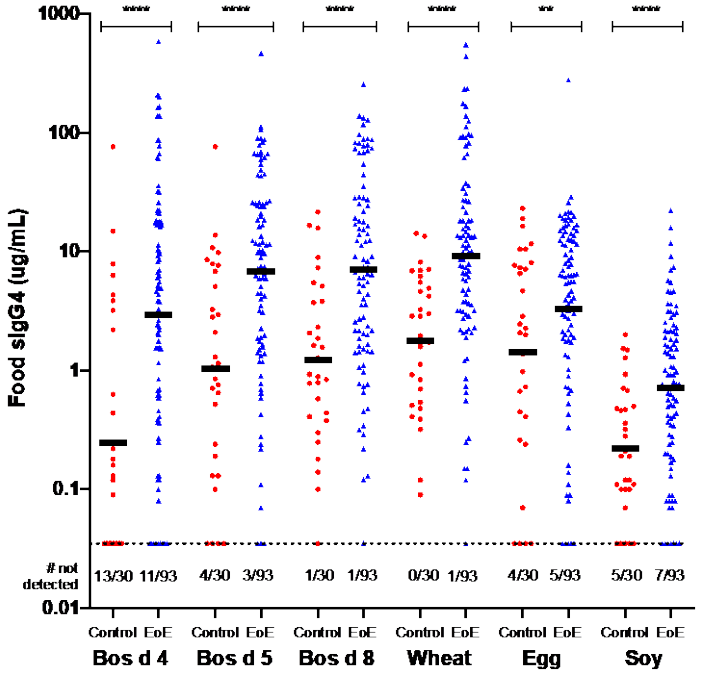
- Established in May 2017, and enrollment is ongoing
- Patients are eligible for enrollment if they are:
  A. Followed in the multidisciplinary EoE clinics (pediatric or adult) OR
  B. Undergoing EGD for evaluation of suspected EoE
- All data is stored in a REDCap database
- 350 patients have enrolled (50% pediatric)

Case-Control Study Results

Table 1: Description of Case Control Study Population

	Controls (n = 30)	EoE (n = 93)	p value
Age†	13 (3 - 77)	20 (1 - 60)	0.03
Male Sex	13 (43)	63 (68)	0.02
Non-Hispanic White	24 (80)	82 (88)	0.12
Allergic History			
Overall	27 (93)	79 (86)	0.30
Asthma	11 (38)	44 (47)	0.45
Allergic Rhinitis	24 (83)	66 (71)	0.44
Eczema	10 (34)	36 (39)	0.87
Food Allergy	13 (45)	43 (46)	0.92
Milk Consumption	28 (93)	67 (73)	0.02

Values expressed as n (%) unless otherwise defined. †Median (range)



McGowan EC *et al, Clin Exp Allergy*, 2022

Lesson #3

- Food sIgG4 levels are higher among patients with EoE than atopic controls
- This is likely due to the unique milieu in EoE, characterized by T2 inflammation and chronic antigen exposure
- Whether IgG4 is an epiphenomenon or pathogenic in EoE is still unknown

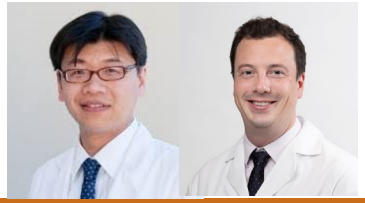
Question

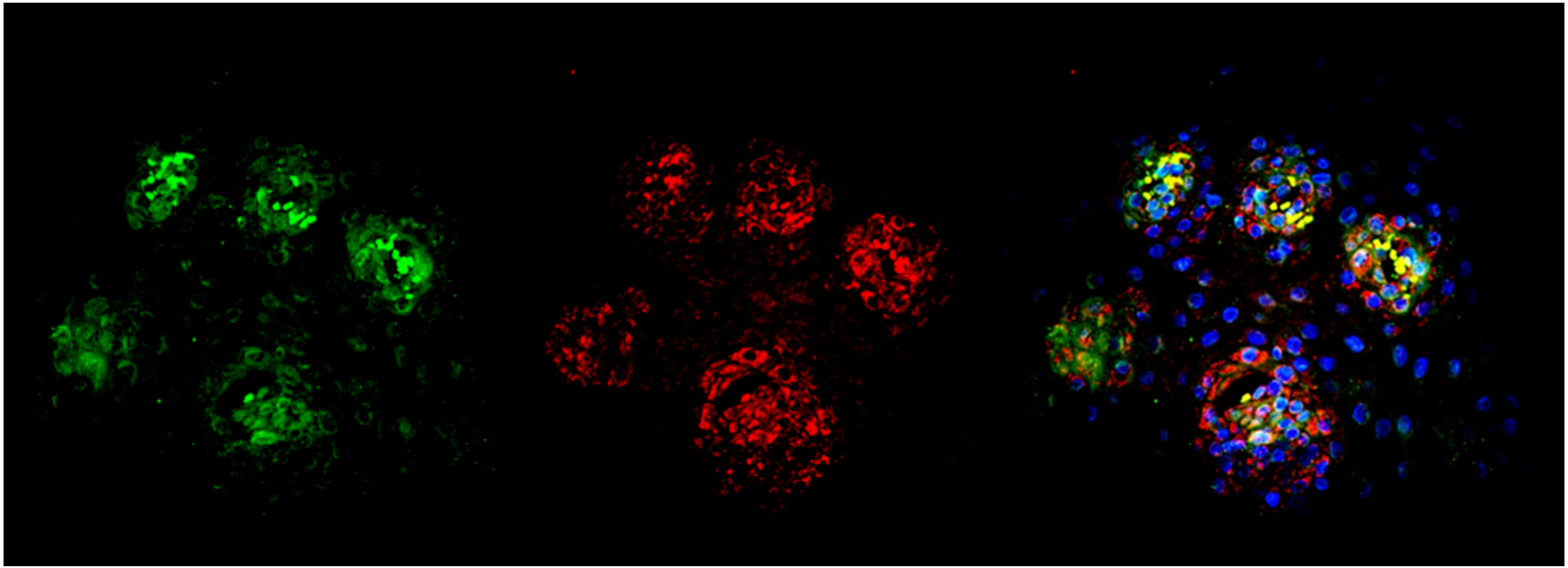
- Why is IgG4 present in the tissue?

Hypothesis

- IgG4 is forming immune complexes with food in esophageal tissue.

IgG4-Wheat Co-Localization

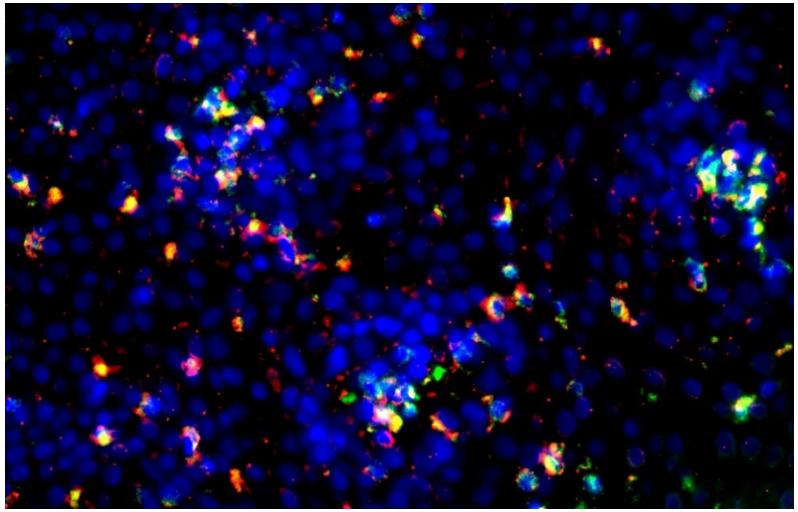




A (Left) FITC green fluorescence with IgG4 primary Antibody; B (Middle) Cy5 red fluorescence with wheat protein; C (Right) Combined Green and red fluorescence plus blue dye (DAPI for nucleus)

Milk and IgG4 Co-localization

Active EoE

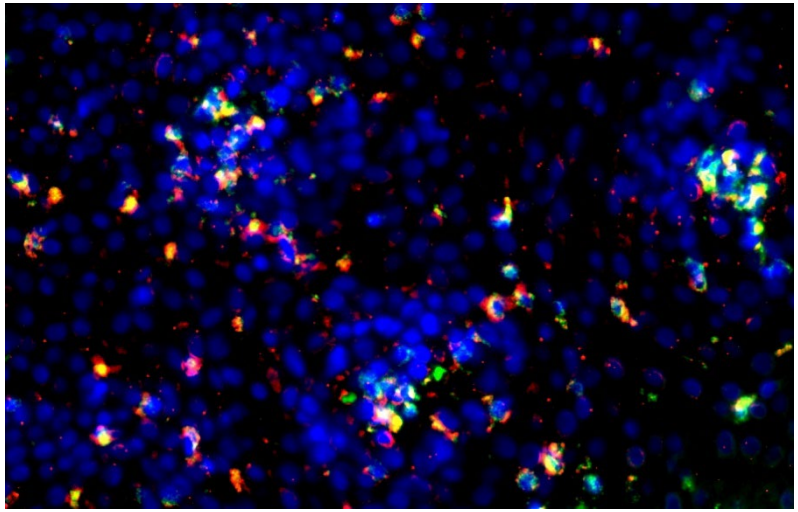


Red = Milk proteins
Blue = DAPI nuclear counterstain
Green = Co-staining for IgG4

Medernach J, *et al,* under review

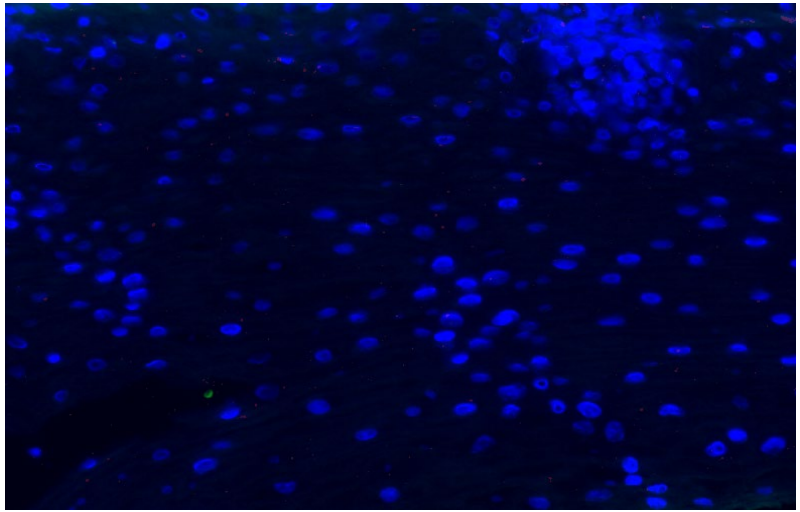
Milk and IgG4 Co-localization

Active EoE



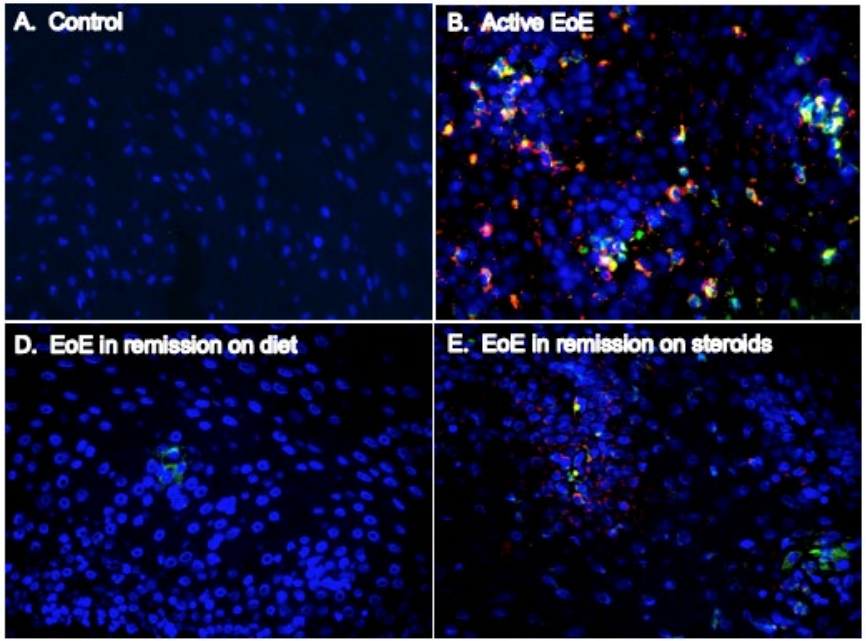
Red = Milk proteins
Blue = DAPI nuclear counterstain
Green = Co-staining for IgG4

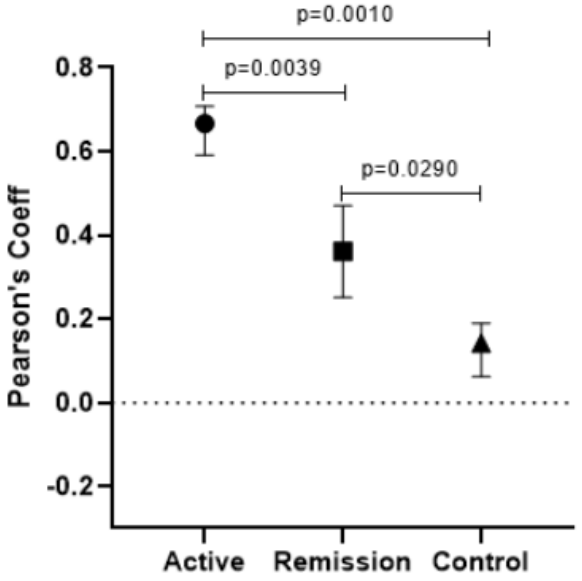
Remission (Same patient)



Medernach J, *et al,* under review

Co-Localization and Disease Activity





Medernach J, *et al,* under review

Co-Immunoprecipitation

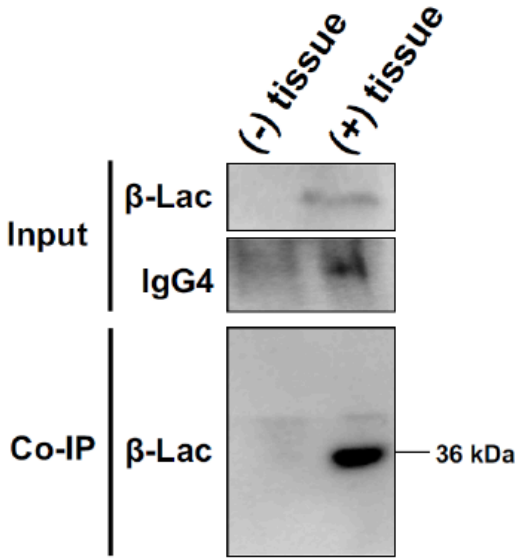
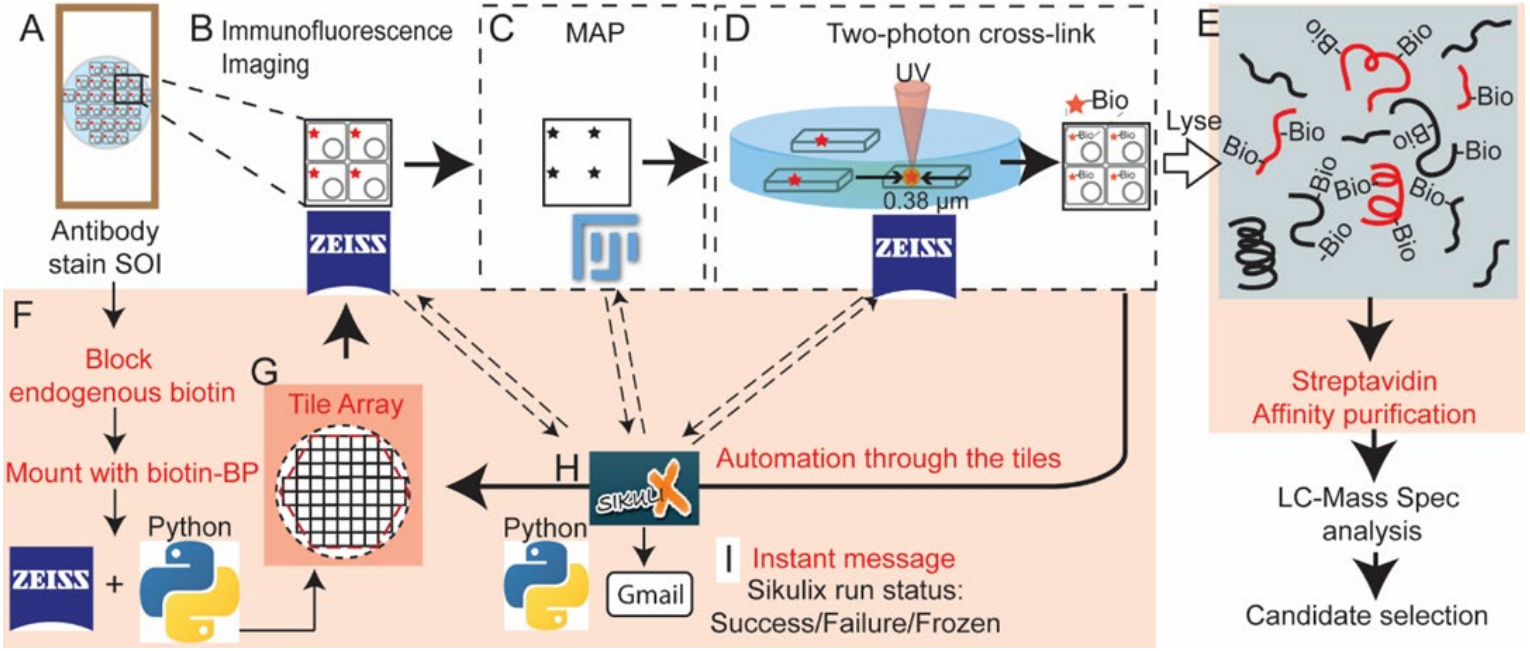


Figure 5: Co-IP of IgG4 and Bos d 5 (β-Lactoglobulin) dimer in a patient with active EoE (+) and non-EoE control (-).

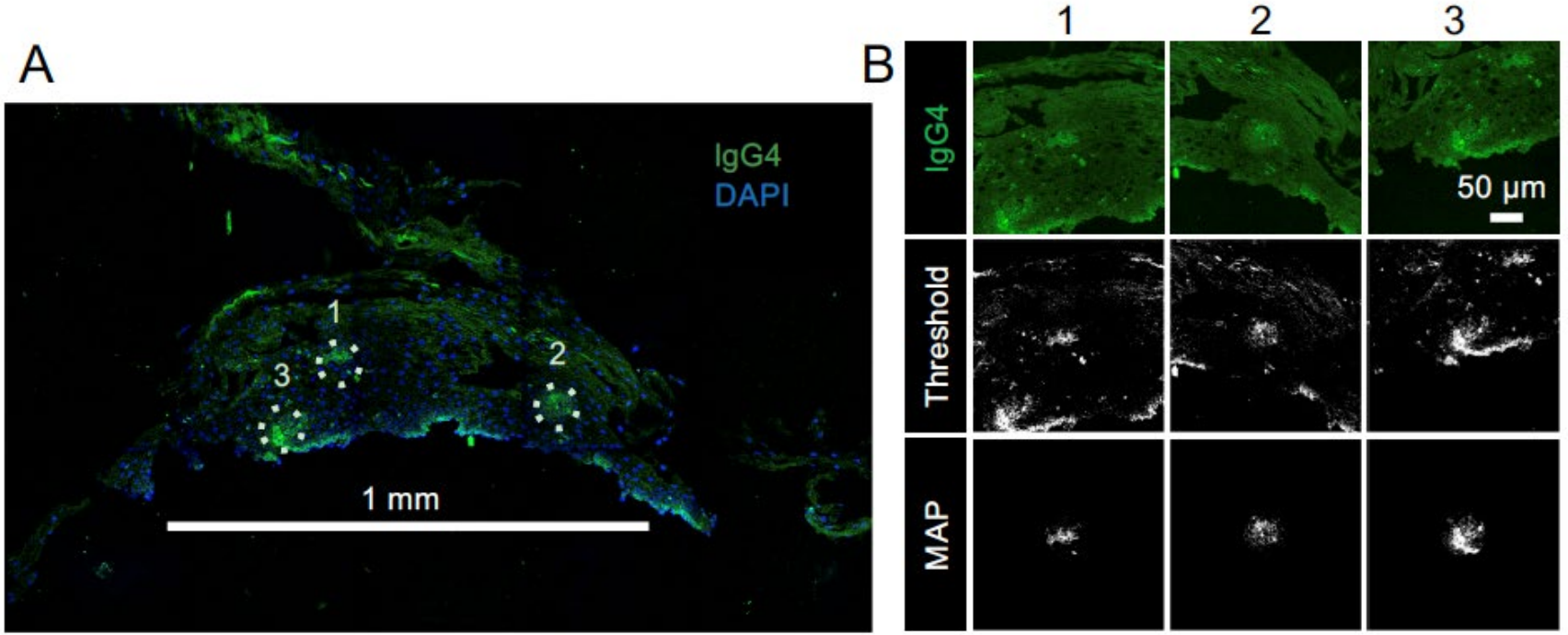
- Allergens identified:
  - Cow's milk (Bos d 5, 6, 10)
  - Almond (Pru du 6)
  - Tuna (enolase)
  - Sesame (Ses I 6)
  - Tilapia (Ore m 4)
  - Pea (Pis s 1)
  - Cherry (Pru av 1)
  - Dust mite (elongation factor 2, Der p 14)

Medernach J, *et al,* under review

Overview of autoSTOMP

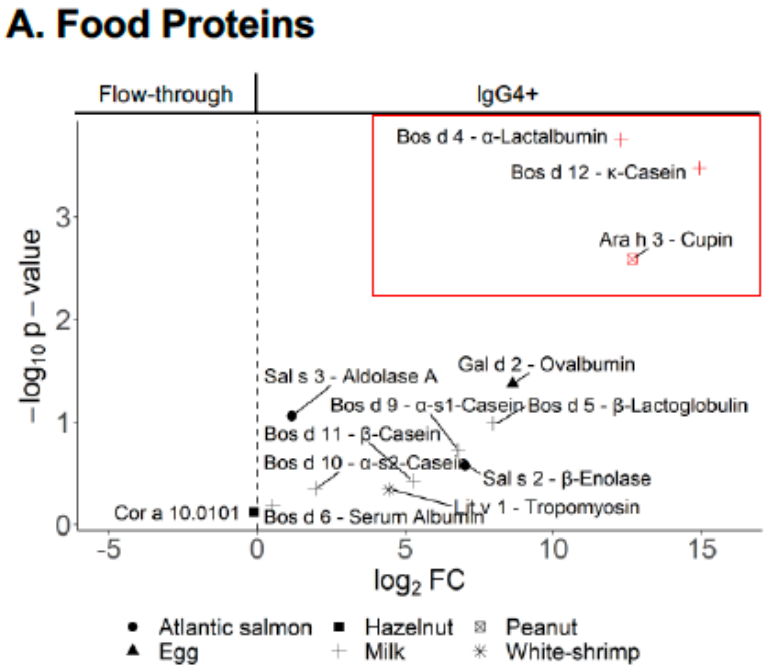


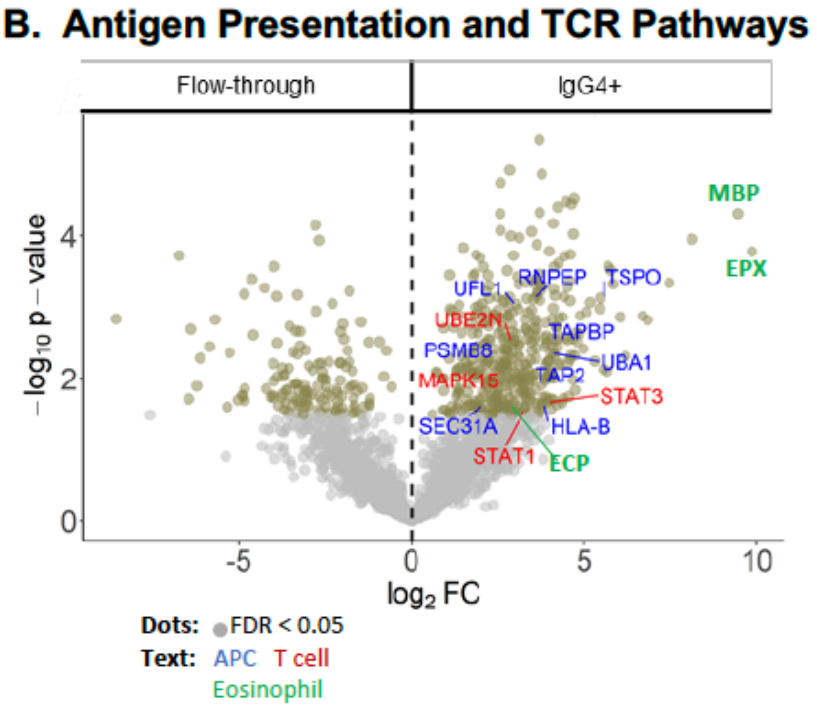
autoSTOMP of EoE Sample



Medernach J, *et al,* under review

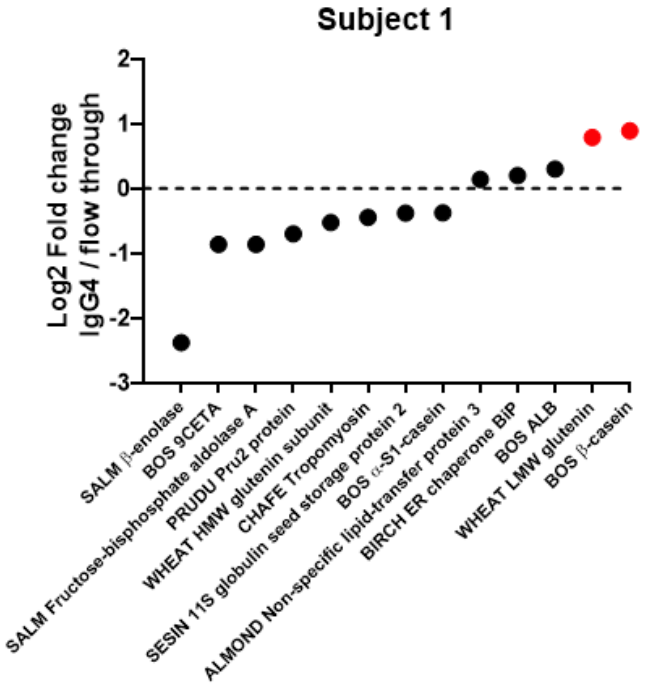
Proteins Enriched Around IgG4

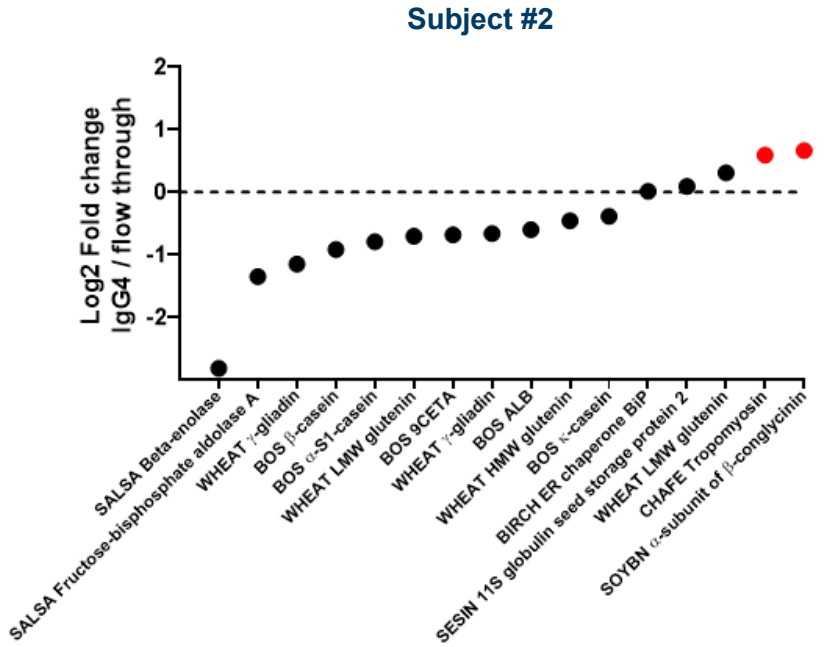




Medernach J, *et al,* under review

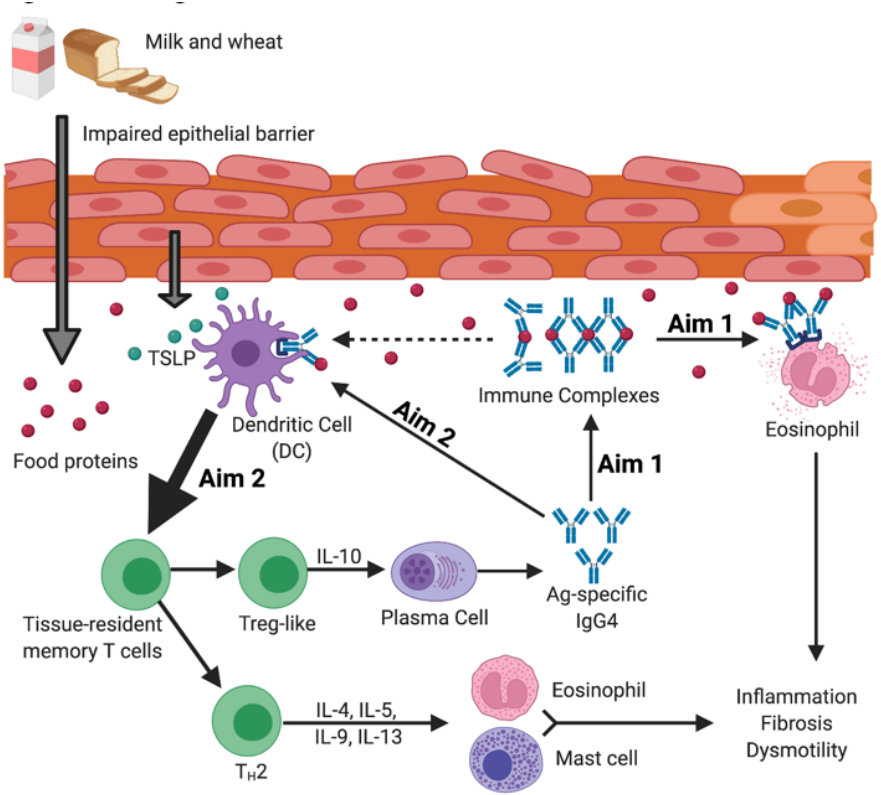
Patient-Specific Pattern of Foods





Medernach J, *et al,* under review

Working Model . . .



Created with biorender.com

Lesson #4

- IgG4 co-localizes with milk and wheat proteins in the esophageal tissue of EoE patients with active disease

- Whether this is pathogenic, however, remains unknown and is the subject of ongoing work . . .

Conclusions

- EoE is less often diagnosed in those with decreased access to care
- EoE is likely underdiagnosed in patients with allergic disease
- Individuals with EoE have very high serum titers of sIgG4 to cow's milk, wheat, and soy proteins
- IgG4 and food proteins appear to co-localize in the esophageal tissue of patients with EoE

Acknowledgements

Division of Asthma, Allergy & Immunology

Jonathan Mednernach, DO
Rung-chi Li, DO PhD
Larry Borish, MD
Thomas Platts-Mills, MD PhD
Elaine Etter, PhD
Jeff Wilson, MD PhD
Behnam Keshararz, PhD
Emily Noonan
Lisa Workman

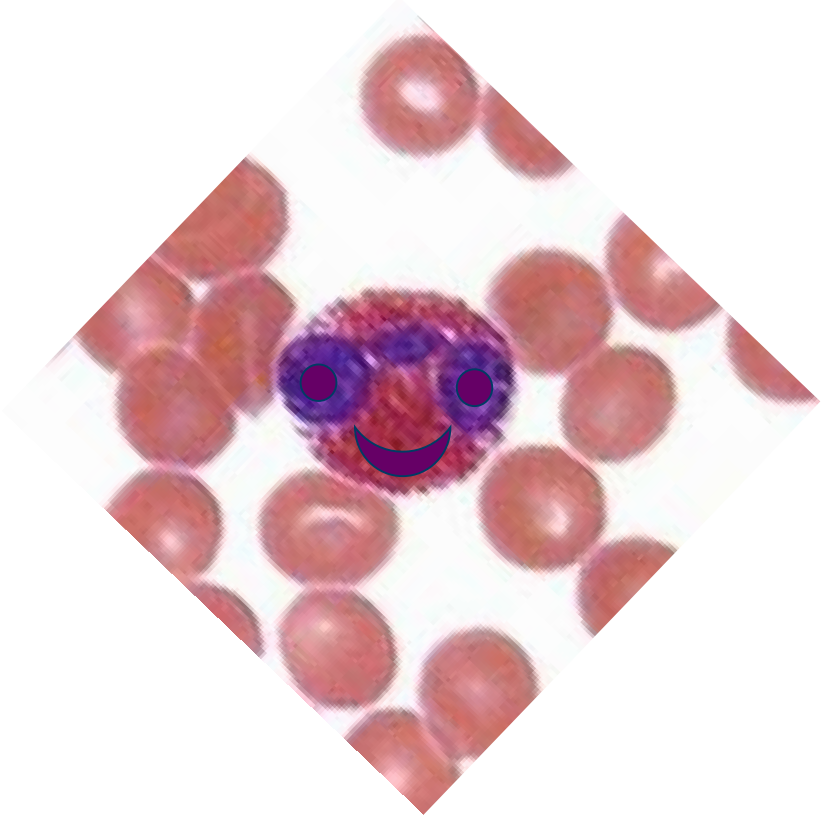
EoE Clinical Team

Barrett Barnes, MD
Bryan Sauer, MD MHS
Beth Woodward, RN
Shyam Raghavan, MD
Tegan Medico, RDN
Caroline Gross, RDN

Department of Microbiology, Immunology, and Cancer Biology

Sarah Ewald, PhD
Bocheng Yin, PhD

Thank You!



Questions?

References

- Arias A, Perez-Martinez I *et al. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies.* Aliment Pharmacol Ther. 2016; 43:3-15
- Arias A, Gonzalez-Cervera J, et al. Efficacy of Dietary Interventions for Inducing Histologic Remission in Patients with Eosinophilic Esophagitis: A systematic Review and Meta-analysis. Gastroenterology. 2014; 146(7): 1639-48.
- Attwood SEA, Smyrk TC, Demeester TC, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci. 1993;38:109–116.
- Brown LF, Goldman H, Antonioli DA. Intraepithelial eosinophils in endoscopic biopsies of adults with reflux esophagitis. Am J Surg Pathol. 1984;8:899–905.
- Davis BP, Stucke EM, Khorki ME, et al. Eosinophilic esophagitis-linked calpain 14 is an IL-13- induced protease that mediates esophageal epithelial barrier impairment. JCI Insight 2016;1:e86355.
- DeBrosse CW, Collins MH, Buckmeier Butz BK, et al. Identification, epidemiology, and chronicity of pediatric esophageal eosinophilia, 1982–1999. J Allergy Clin Immunol. 2010;126:112–119.

References (cont)

- Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA; American College of Gastroenterology. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastro, 2013 May;108(5):679-92; quiz 693. doi: 10.1038/ajg.2013.71. Epub 2013 Apr 9
- Dellon ES. Epidemiology of Eosinophilic Esophagitis. Gastroenterol Clin North Am. 2014; Jun 43(2): 201-218
- Dellon ES, Speck O, Woodward K, et al. Clinical and Endoscopic Characteristics do Not Reliably Differentiate PPI-Responsive Esophageal Eosinophilia and Eosinophilic Esophagitis in Patients Undergoing Upper Endoscopy: A Prospective Cohort Study. Am J Gastroenterol. 2013;108:1854–1860
- Dobbins JW, Dheahan DG, Behar J. Eosinophilic gastroenteritis with esophageal involvement. Gastroenterology. 1977 Jun; 72(6): 1312-6.
- Erwin E, *et al.* IgE antibodies and response to cow's milk elimination diet in pediatric eosinophilic esophagitis. JACI. 2016. 138(2): 625-628.
- Faubion WA, Jr, Perrault J, Burgart LJ, et al. Treatment of eosinophilic esophagitis with inhaled corticosteroids. J Pediatr Gastroenterol Nutr. 1998;27:90–3.
- Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME; First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees. Gastroenterology. 2007 Oct;133(4):1342-63. Epub 2007 Aug 8. Review.

References (cont)

- González-Cervera J, Arias Á, Redondo-González O, Cano-Mollinedo MM, Terreehorst I, Lucendo AJ. Association between atopic manifestations and eosinophilic esophagitis: a systematic review and meta-analysis. Ann Allergy Asthma Immunol; 2017, 118(5):582–590.e2
- Gonsalves N, Yang GY, *et al.* Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology 2012; 142(7): 151-9
- Hill DA, Dudley JW, Spergel JM. The prevalence of eosinophilic esophagitis in pediatric patients with IgE mediated food allergy. J Allergy Clin Immunol Pract; 2017;5:369–375.
- Hiremath GS, Hameed F, Pacheco A, et al. Esophageal food impaction and eosinophilic esophagitis: a retrospective study, systematic review, and meta-analysis. Dig Dis Sci 2015;60:3181–3193.
- Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology. 1995;109:1503–12.
- Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, Collins MH, Dellon ES, Dohil R, Falk GW, Gonsalves N, Gupta SK, Katzka DA, Lucendo AJ, Markowitz JE, Noel RJ, Odze RD, Putnam PE, Richter JE, Romero Y, Ruchelli E, Sampson HA, Schoepfer A, Shaheen NJ, Sicherer SH, Spechler S, Spergel JM, Straumann A, Wershil BK, Rothenberg ME, Aceves SS. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011 Jul;128(1):3-20.e6; quiz 21-2. doi: 10.1016/j.jaci.2011.02.040. Epub 2011 Apr 7. Review.

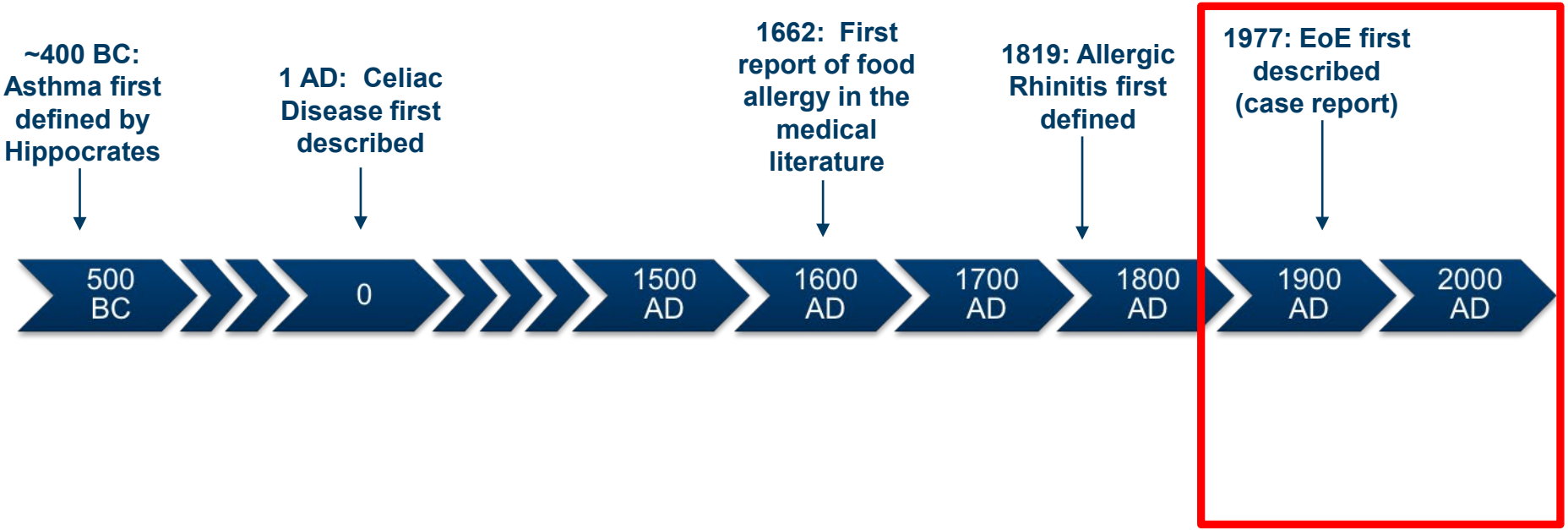
References (cont)

- Lucendo AJ *et al*. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterology journal. 2017; 5(3): 335-358
- Molina-Infante J, Zamorano J. Distinguishing eosinophilic esophagitis from gastroesophageal reflux disease upon PPI refractoriness: what about PPI-responsive esophageal eosinophilia? Digestion. 2012;85:210.
- Molina-Infante J, Matin-Noguerol E, et al. Selective elimination diet based on skin testing has suboptimal efficacy for adult eosinophilic esophagitis. J Allergy Clin Immunol 2012; 130(5): 1200-02
- Molina-InfanteJ, Arias A, Barrio J, *et al.* Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. J Allergy Clin Immunol 2014; 134(5): 1093-9
- O'Shea, Aceves SS, Dellon ES, Gupta SK, Spergel JM, Furuta GT, Rothenberg ME. Pathophysiology of Eosinophilic Esophagitis. Gastroenterology. 2017. Jul 27. [Epub ahead of print]
- Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. Am J Gastroenterol 2013; 108: 759-66.
- Prasad GA, Talley NJ, Romero Y, et al. Prevalence and predictive factors of eosinophilic esophagitis in patients presenting with dysphagia: a prospective study. Am J Gastroenterol 2007;102:2627–2632.
- Rodriguez-Sanchez J, Gomez Torrijos E, et al. Efficacy of IgE-targeted vs empiric six-food elimination diets for adult eosinophilic esophagitis. Allergy 2014; 69(7): 936-42.

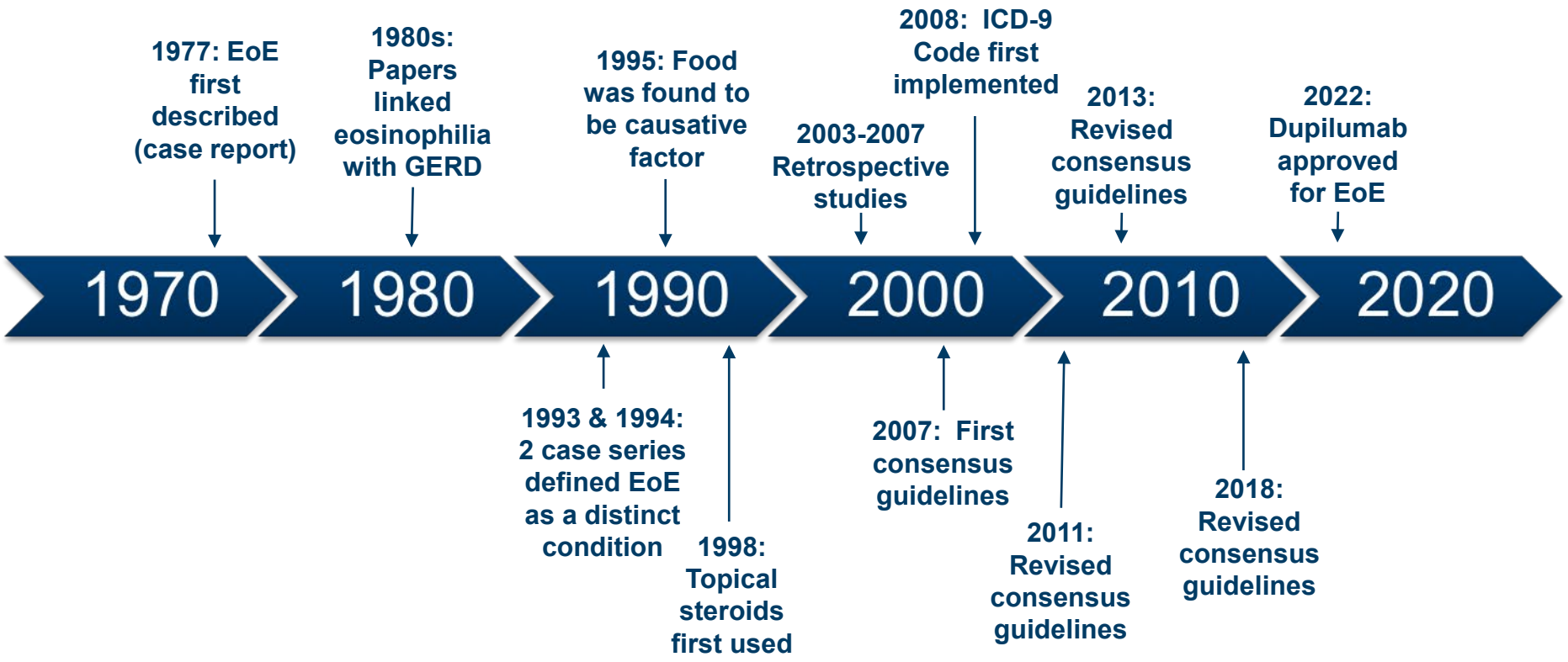
References (cont)

- Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. J Allergy Clin Immunol 2015;135:500-7.
- Rothenberg ME. Molecular, genetic, and cellular bases for treating eosinophilic esophagitis. Gastroenterology; 2015;148:1143–1157.
- Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunology 2012; 130: p 461-7.
- Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013;145:1230–1236.e2.
- Straumann A, Spichtin HP, Bernoulli R, et al. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings. Schweiz Med Wochenschr. 1994;124:1419–29.
- Straumann A, Spichtin HP, Grize L, et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology; 2003;125:1660–1669.
- Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011;9:400–409.e1.
- Whitney-Miller CL, Katzka D, Furth EE. Eosinophilic esophagitis: a retrospective review of esophageal biopsy specimens from 1992 to 2004 at an adult academic medical center. Am J Clin Pathol. 2009;131:788–792.

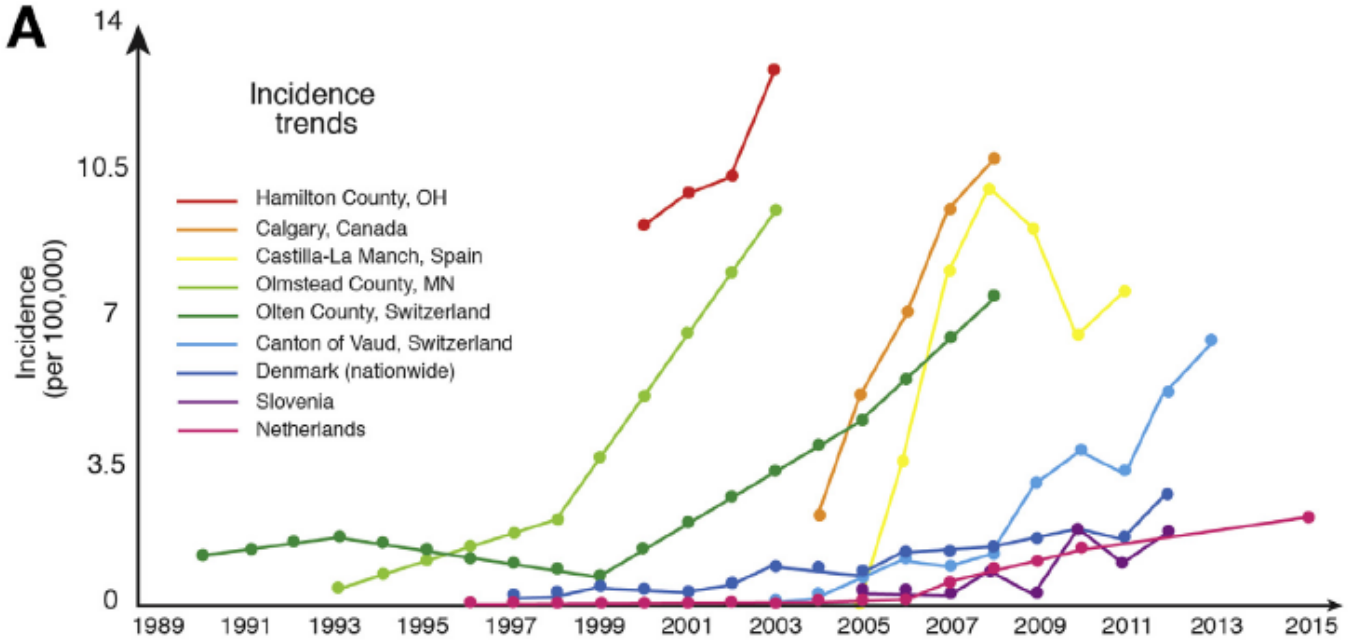
Timeline of Allergic Disease



History of EoE



EoE Appears to be Increasing



Dellon ES, *Gastroenterology*, 2018

Evidence for a True Increase

Diagnosis Outpaces Biopsies

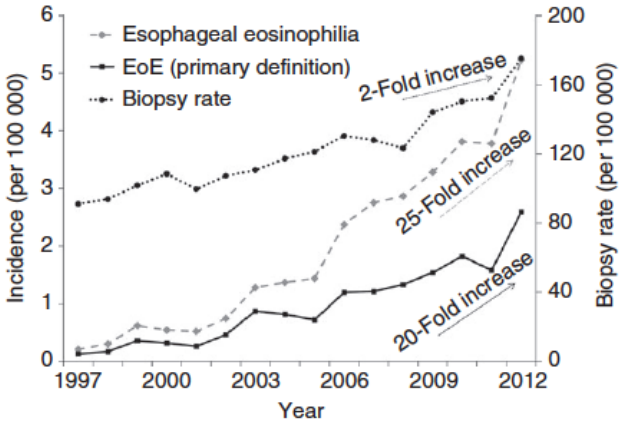
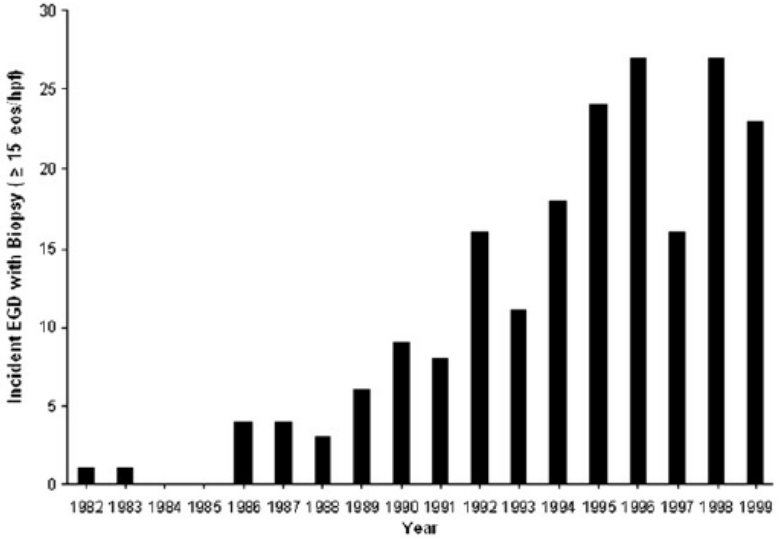


Figure 4 | Comparison of oesophageal eosinophilia and EoE incidence to oesophageal biopsy rates in Denmark.

Dellon ES *et al,* AP&T, 2015

EoE Not Missed in the Past



DeBrosse CW *et al,* JACI, 2010

Milk Component sIgG4 Levels

	No	Yes	P value
Age ≥ 18	129.6 ± 216.5	55.7 ± 69.0	0.32
Male Sex	81.6 ± 97.6	94.1 ± 179.4	0.68
White Race/Ethnicity	75.8 ± 97.2	92.4 ± 166.7	0.85
Allergic History	**111.8 ± 104.7**	**87.1 ± 168.9**	**0.06**
PPI Treatment	111.2 ± 215.1	72.2 ± 85.1	0.95
SS Treatment	140.9 ± 276.8	74.0 ± 93.3	0.39
Milk Consumption	**41.5 ± 77.9**	**109.4 ± 181.1**	**0.002**
Fibrostenosis	135.4 ± 259.8	72.4 ± 92.2	0.49

Values expressed as mean ± SD

Li RC, McGowan EC, unpublished data

UVA EoE Cohort (continued)

Clinical Database

- Exposures
- Atopic/Medical History
- Family/Dietary History
- Treatment
- Pathology/Lab values
- EREFS Scores
- Validated Symptom Scores (PEESS, EASI)

Biorepository

- Serum
- Esophageal Tissue
- Saliva
- Urine
- PBMCs (subset)

Typical Symptoms

Children

- Feeding dysfunction (~2y)
- Vomiting (~8y)
- Abdominal pain (~12y)
- Dysphagia (~13y)
- Food impaction (~17y)

Adults

- Dysphagia
- Food impaction
- Chest pain
- Heartburn
- Upper abdominal pain
- Esophageal perforation

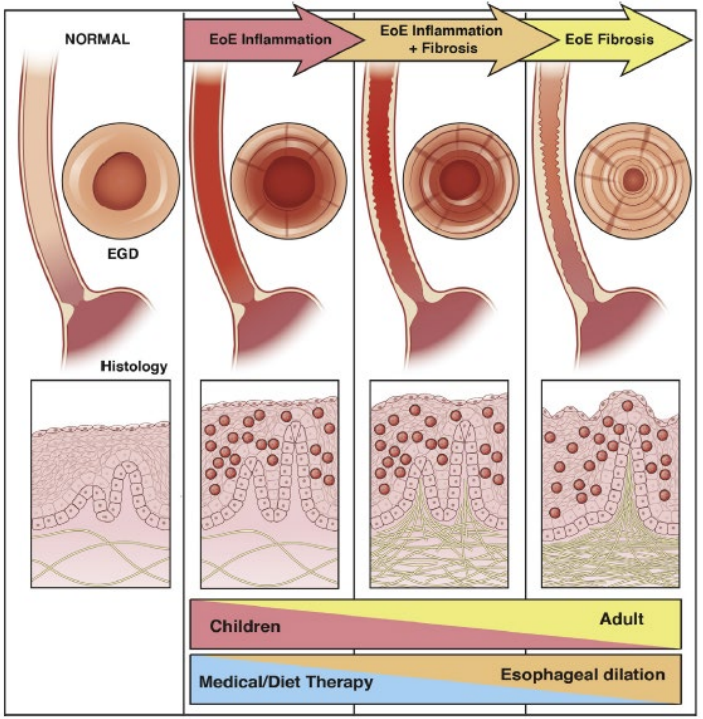
Natural History

- Diagnosis is typically delayed (average 4.6 years)
- Considered a chronic disease
  - EoE does not typically spontaneously resolve
  - EoE recurs in most patients when treatment is stopped
- No reports of transformation to hypereosinophilic syndrome (HES), extension to other areas of GI tract, or malignancy

Straumann A *et al*, Gastroenterology 2003
Straumann A *et al,* Clin Gastro Hep, 2011
Schoepfer AM, *et al,* Gastroenterology, 2013

Progression to Fibrosis

- Thought to progress from inflammation to fibrosis
  - ~2 years of symptoms: 17% had strictures
  - ~20 years of symptoms: 70% had strictures



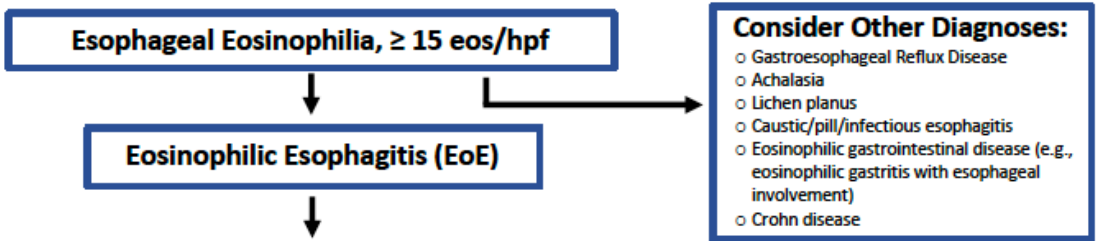
Schoepfer AM, *et al,* Gastroenterology, 2013
Dellon ES, *Gastroenterology,* 2018

Treatment Options

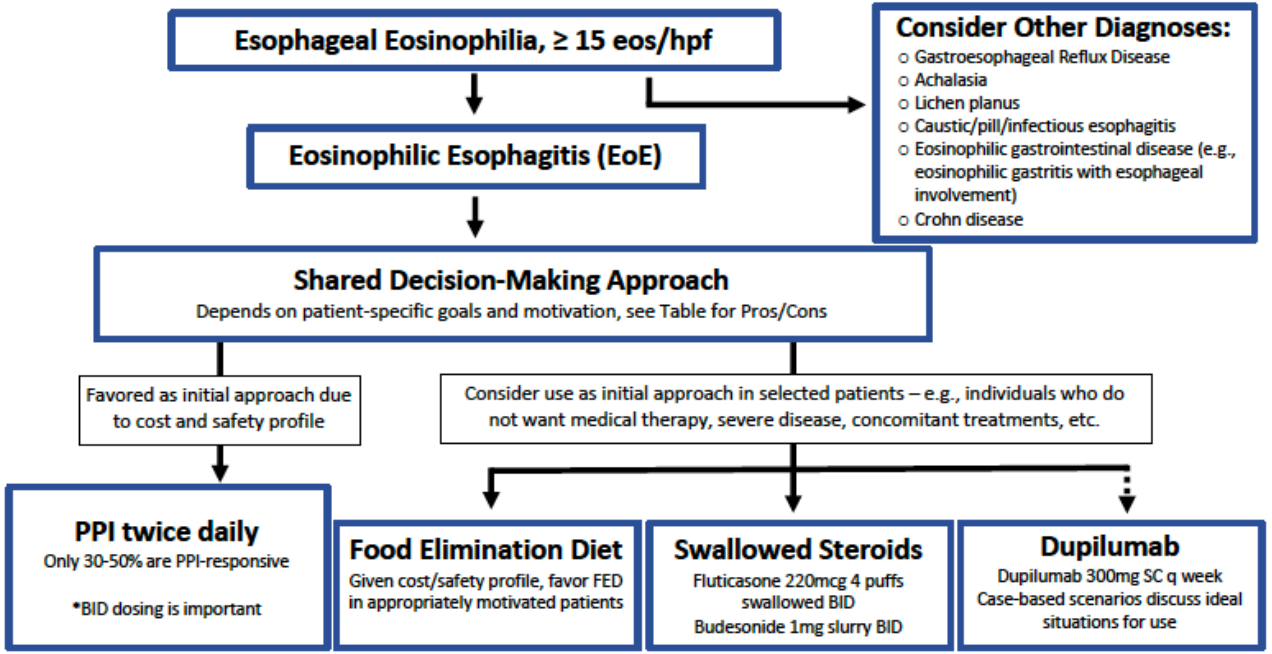
Treatment	Dose frequency	Cost	Side Effects*	Side effect profile	Pros	Cons
Proton pump inhibitor	Once to twice daily	$	Headache, diarrhea, increased risk of enteric infections	Low	Low cost, well tolerated	Once or twice daily medication, only 30-50% response rate

Treatment Options

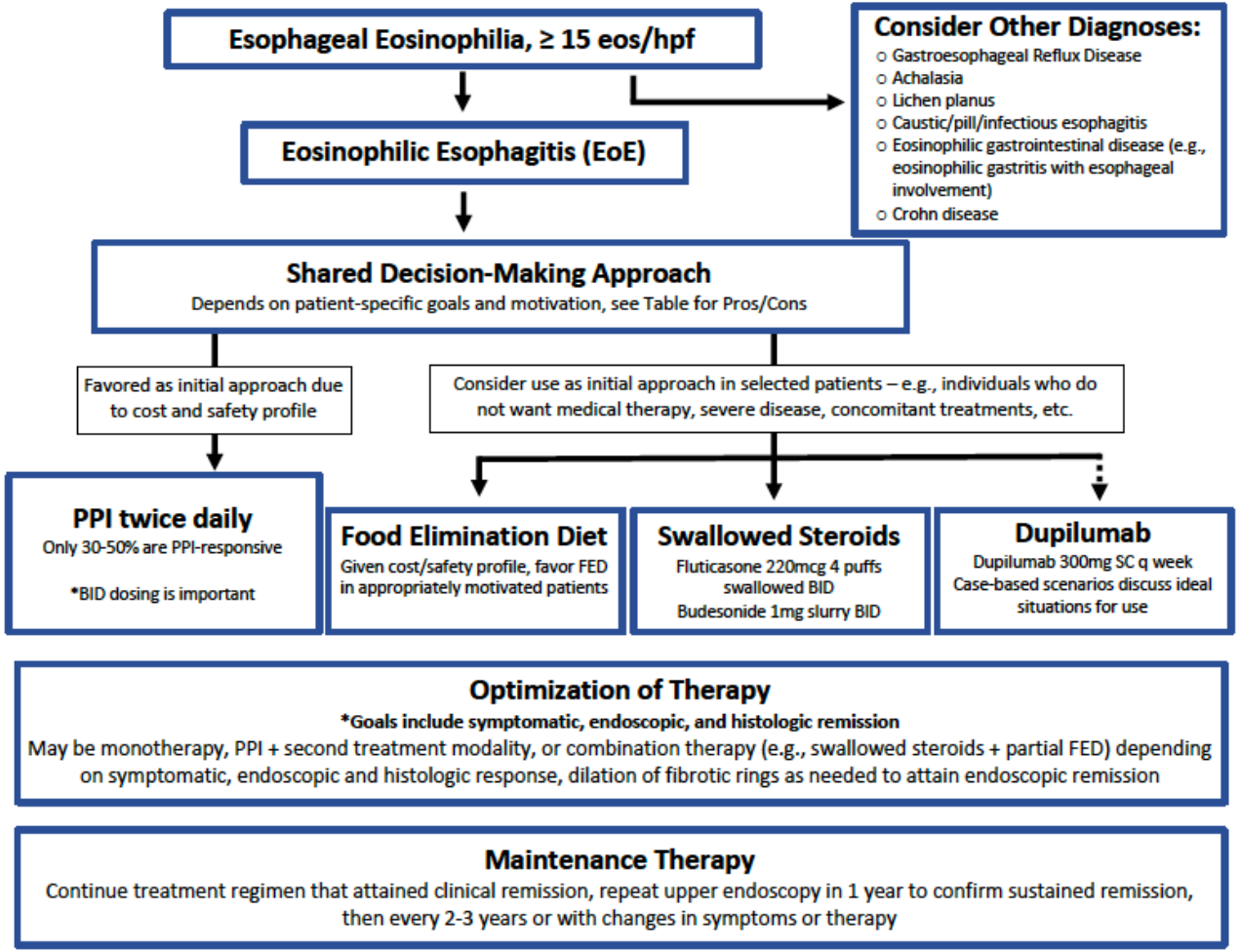
1. Proton Pump Inhibitors (PPI)
2. Swallowed Steroids
3. Dietary Therapy
4. Esophageal Dilations
5. Dupilumab



Sauer BS, McGowan EC, *Am J Gastro, 2023*



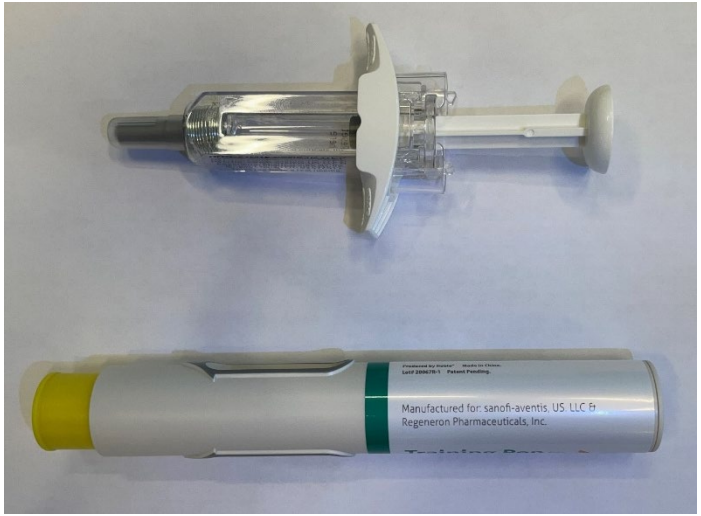
Sauer BS, McGowan EC, *Am J Gastro, 2023*



Sauer BS, McGowan EC, *Am J Gastro, 2023*

UVA Approach to Dupilumab

- Other allergic conditions (eczema, asthma, CRSwNP)
- Side effects from swallowed steroids
- Non-compliance
- Non-responders
- Severe disease?



Drivers of High IgG4 Levels

Table 2: Associations Between Clinical Characteristics and Milk sIgG4 >30 µg/mL

	Crude OR	p value	Adjusted OR	p value
Age < 18	1.21 (0.53 – 2.75)	0.65	1.32 (0.45 – 3.85)	0.62
Male Sex	1.55 (0.64 – 3.74)	0.33	2.00 (0.66 – 6.03)	0.22
Race/ethnicity	1.13 (0.80 – 1.58)	0.49	1.19 (0.83 – 1.72)	0.35
Atopic History	0.72 (0.22 – 2.33)	0.58	0.57 (0.14 – 2.35)	0.44
Fibrostenotic Disease	1.30 (0.49 – 3.44)	0.60	0.86 (0.28 – 2.70)	0.80
Peak eos/hpf	0.99 (0.96 – 1.02)	0.56	0.98 (0.95 – 1.01)	0.20
Milk consumption	**4.15 (1.47 – 11.7)**	**0.007**	**5.03 (1.51 – 16.8)**	**0.009**
Positive Milk sIgE	**4.68 (1.75 – 12.5)**	**0.002**	**4.83 (1.61 – 14.6)**	**0.005**

McGowan EC *et al, Clin Exp Allergy*, 2022

Proposed Model