PUBLIC WORKSHOP

U.S. FOOD & DRUG ADMINISTRATION

Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI):

Workshop on Eosinophilic Gastrointestinal Disorders Beyond EoE

July 21, 2021

Division of Gastroenterology (DG)
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research, FDA

GREAT VI WORKSHOP STEERING COMMITTEE

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Jessica J. Lee, MD, MMSc Director Division of Gastroenterology	**Juli Tomaino, MD, MS** Deputy Director Division of Gastroenterology
Erica Lyons, MD, FAAP Associate Director for Therapeutic Review Division of Gastroenterology	**Matthew Kowalik, MD** Team Leader Division of Gastroenterology
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Steering Committee Organizational Representatives	
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American Gastroenterological Association (AGA) **Ikuo Hirano, MD** Northwestern University	**Biotechnology Innovation Organization (BIO)** **Veronica Mas Casullo, MD** Regeneron
Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) **Nirmala Gonsalves, MD** Northwestern University	**North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)** **Calies Menard-Katcher, MD** Children's Hospital of Colorado

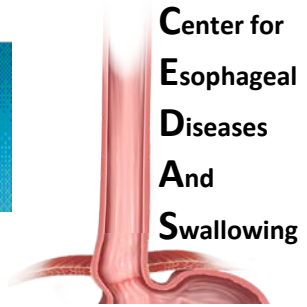
SESSION 1- DIAGNOSIS AND NATURAL HISTORY OF EGID

EGID pathogenesis and nomenclature

FDA GREAT VI Workshop

July 21, 2021

Evan S. Dellon, MD, MPH



Disclosures

Research funding: NIH, ACG, AGA, CURED, Adare/Ellodi, Allakos, AstraZeneca, Celgene/Receptos/BMS, GSK, Meritage, Miraca, Nutricia, Regeneron, Shire/Takeda, UNC/NCTraCS

Consultant: Abbott, Abbvie, Adare/Ellodi, Aimmune, Allakos, Amgen, Arena, AstraZeneca, Avir, Biorasi, Calypso, Celgene/Receptos/BMS, Celldex, Eli Lilly, EosCap, GSK, Gossamer Bio, Landos, Morphic, Parexel/Calyx, Regeneron, Robarts/Alimentiv, Salix, Sanfoi, Shire/Takeda

Educational grant: Allakos, Banner, Holoclara

Objectives

- Define EGIDs and review the general framework for diagnosis
- Discuss EGID nomenclature and ongoing efforts for standardization
- Review EGID pathogenesis
- Provide context for the remainder of the discussion today

What is an EGID?

Analogy with the conceptual definition of 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"

Liacouras et al, JACI, 2011

What is an EGID?

An eosinophilic gastrointestinal disorder is a chronic, immune-mediated disease characterized clinically by GI symptoms and histologically by pathologically increased eosinophil-predominant inflammation

What is an EGID?

An eosinophilic gastrointestinal disorder is a chronic, immune-mediated disease characterized clinically by GI symptoms and histologically by pathologically increased eosinophil-predominant inflammation

This impacts thinking about treatment outcomes and endpoints! What does it mean for tissues where eosinophils are normally present, and can we move away from a focus “The Number”?

What is an EGID?

We will hear today:

- Symptoms are well characterized (though non-specific)
- Natural history described
- Histologic features described
- Genetic features beginning to be described
- Epidemiology being understood
- Rapidly increasing knowledge base

Knowledge base for drug development may be different than for clinical practice

The diagnostic approach in practice

Even without consensus diagnostic guidelines, the approach to diagnosis in individual patients is known:

Symptoms of organ dysfunction

Additional supportive findings:
- Clinical features/phenotype
- Endoscopic features
- Biomarkers/molecular features

Abnormally high levels of mucosal eosinophilia*

Evaluation of potential competing causes of eosinophilia

EGID Diagnosis

*determination and testing of specific thresholds is underway

Epidemiology of non-EoE EGID

Non-EoE EGIDs are currently classified as rare diseases

Prevalence estimates from large administrative databases:

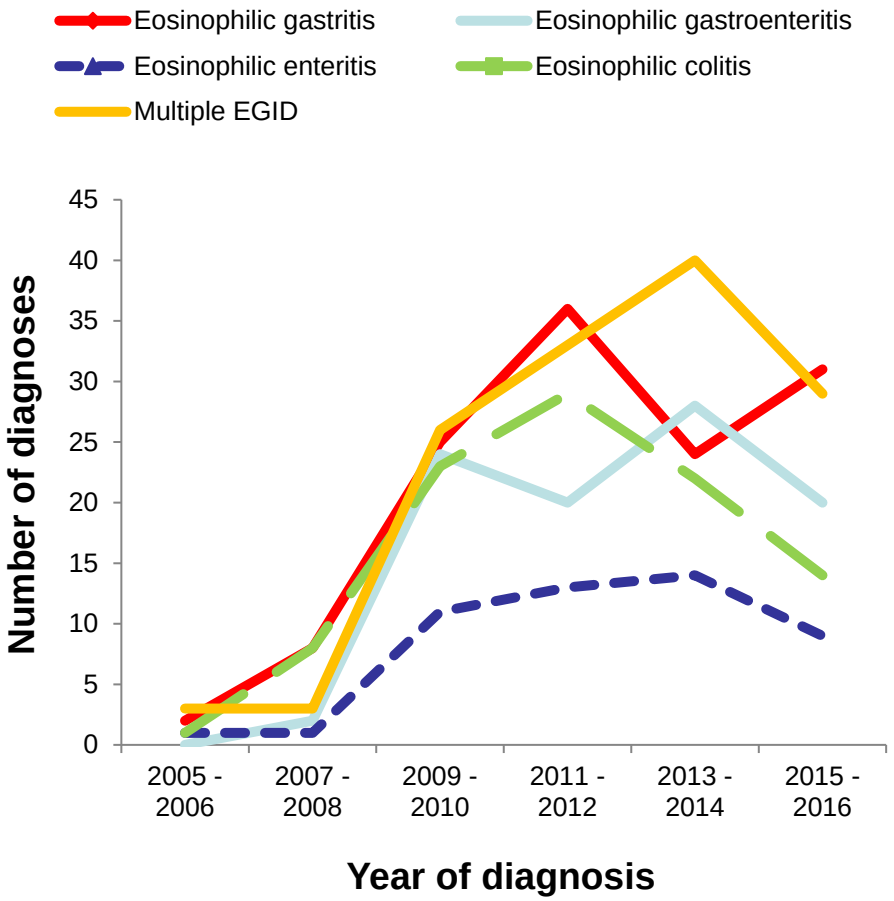
- EG: 6.4/100,000
- EGE: 5.1 - 8.3/100,000
- EC: 2.1 - 3.5/100,000

Total number of non-EoE EGIDs in the U.S. ~ 49,000

Jensen et al, JPGN, 2015; Mansoor et al, CGH, 2017

Epidemiology of non-EoE EGID

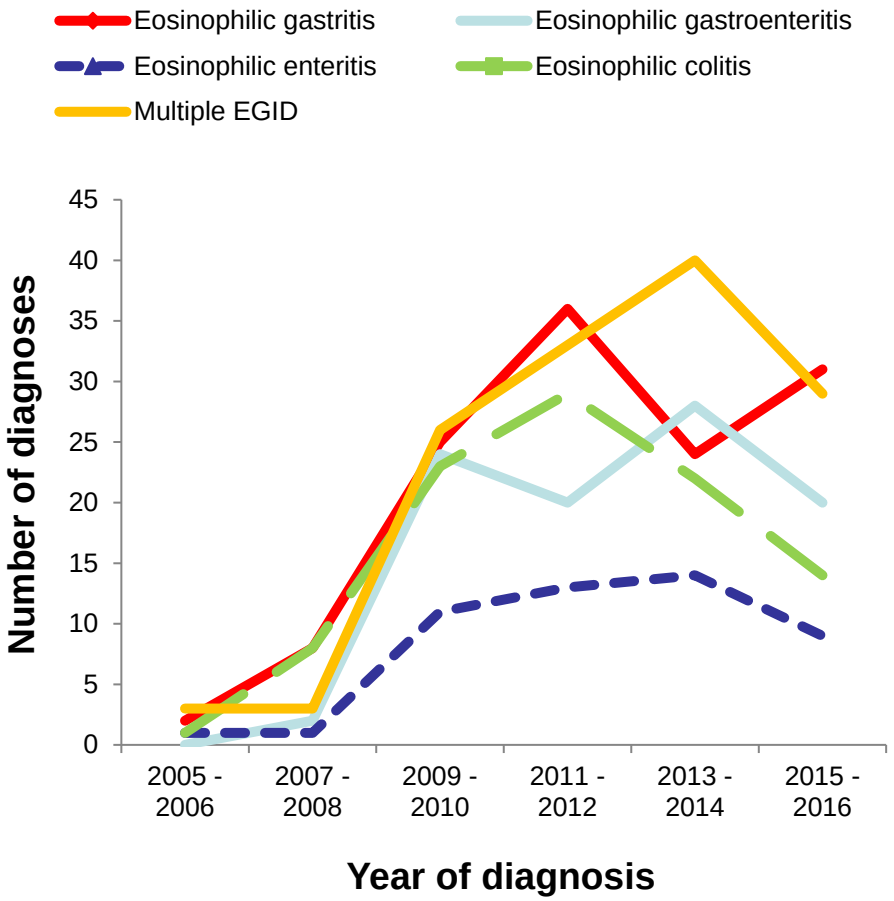
On the rise? Multicenter retrospective study (CEGIR) of 376 EGID patients:*



*Pesek et al, AJG, 2019; **Chehade et al, JACI-IP, 2021; ***Talley et al, DDW, 2021

Epidemiology of non-EoE EGID

On the rise? Multicenter retrospective study (CEGIR) of 376 EGID patients:*

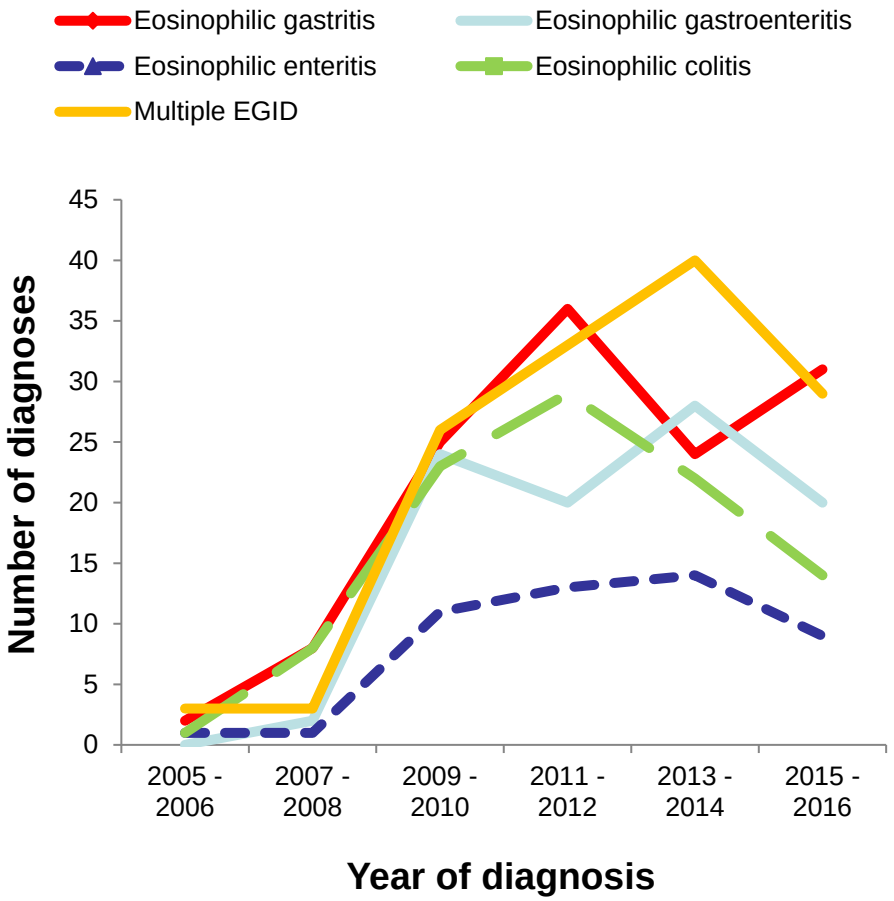


Diagnostic delay of ~ 4 years and possibility of under-diagnosis persists**

*Pesek et al, AJG, 2019; **Chehade et al, JACI-IP, 2021; ***Talley et al, DDW, 2021

Epidemiology of non-EoE EGID

On the rise? Multicenter retrospective study (CEGIR) of 376 EGID patients:*



Diagnostic delay of ~ 4 years and possibility of under-diagnosis persists**

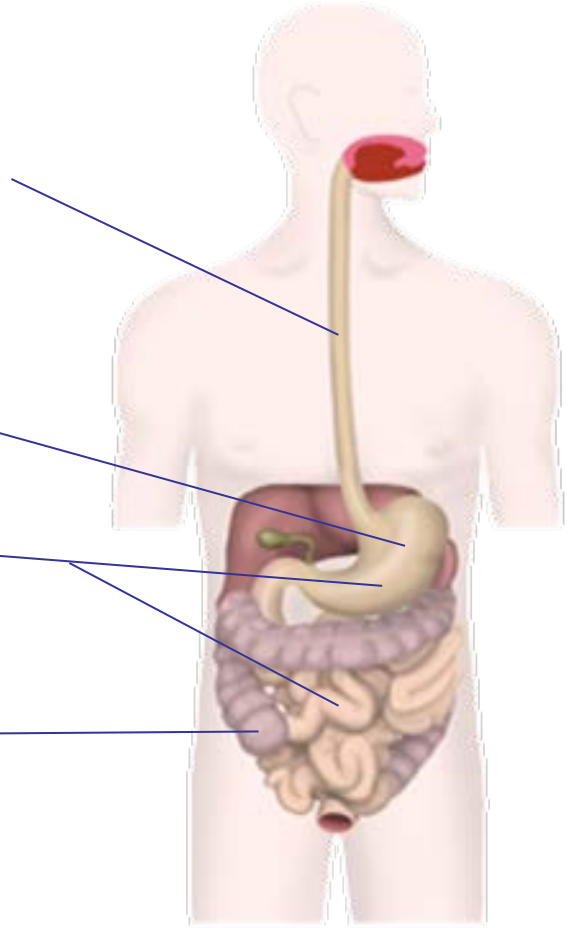
Higher prevalence in a sub-population***

- Prospective multi-center study
- 118/405 subjects (45%) with moderate-severe symptom criteria and EGD with 8 gastric and 4 duodenal biopsies met histologic criteria for EG/EoD

*Pesek et al, AJG, 2019; **Chehade et al, JACI-IP, 2021; ***Talley et al, DDW, 2021

Traditional classification of the EGIDs

- Eosinophilic esophagitis (EoE)
- Eosinophilic gastritis
- Eosinophilic gastroenteritis
- Eosinophilic colitis



Updating EGID nomenclature

Heterogeneity in terminology – particularly with “eosinophilic gastroenteritis”

- Variability in clinical use
- Variability in the literature

} Gastric only? Gastric + duodenum? Duodenum only?

- Majority of “eosinophilic gastroenteritis” papers report duodenal involvement (ie EGD only takes duodenal biopsies, so the “enteritis” is actually “duodenitis”)*

Leads to imprecision both in clinical practice and in research

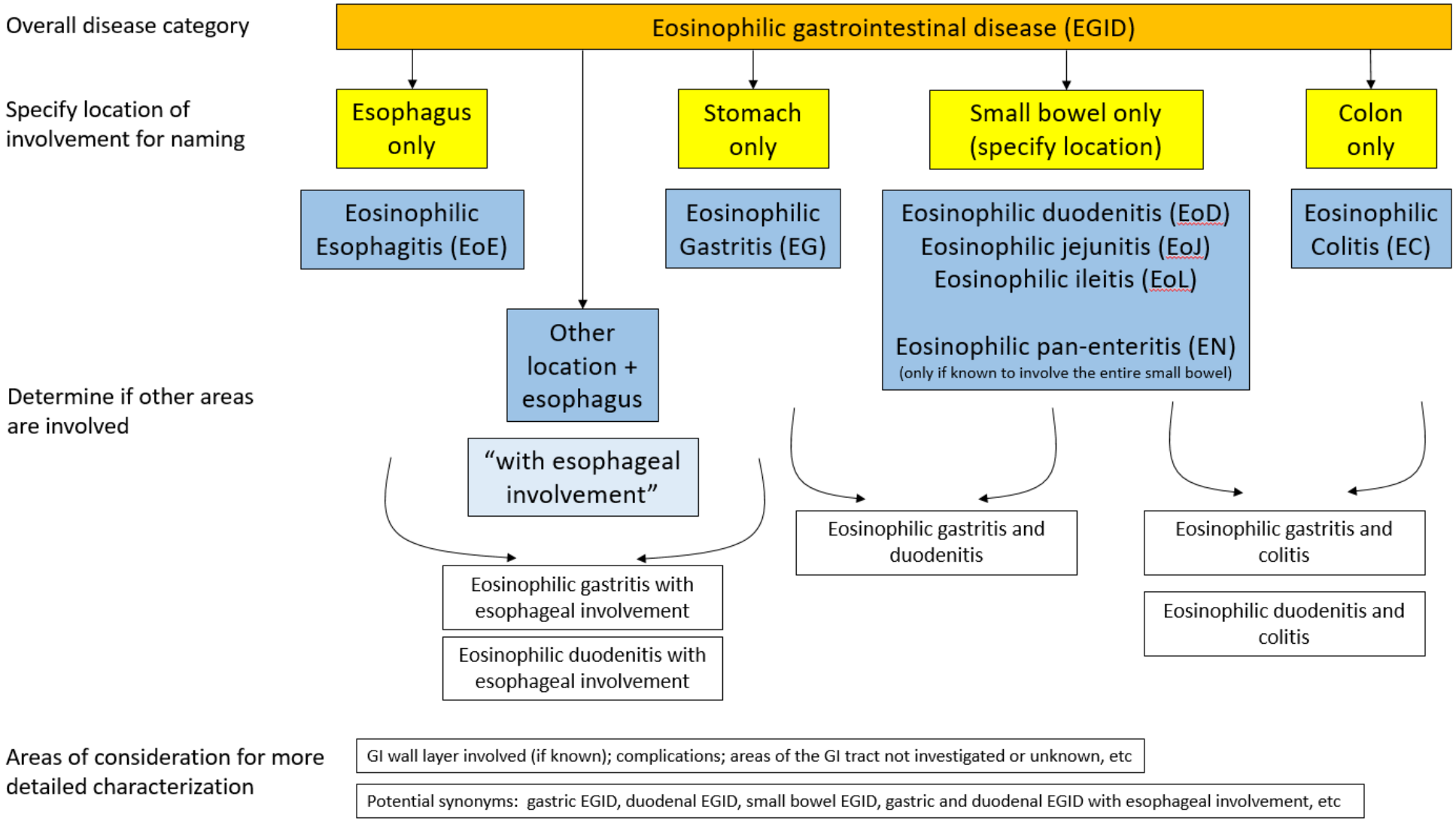
Need standardization (a common language for disease names) before we can put forth formal diagnostic and management guidelines

**Chehade et al; systematic review underway*

Updating EGID nomenclature

- International consensus process, including stakeholders
  - Completed initial Delphi round with 85 participants
    - Experts on 5 continents (NA, SA, Europe, Asia, Australia)
    - GI, allergy, pathology, adult and pediatric providers, range of researchers
- Retain existing nomenclature when possible
- Consider removal or redefinition of the term “eosinophilic gastroenteritis”
- Consider a “two-tier” framework:
  - Create nomenclature that will be useful for clinical practice
  - Include more detailed nomenclature options for research use
- Expectation that nomenclature can and will change in the future, as informed by emerging data

Updating EGID nomenclature

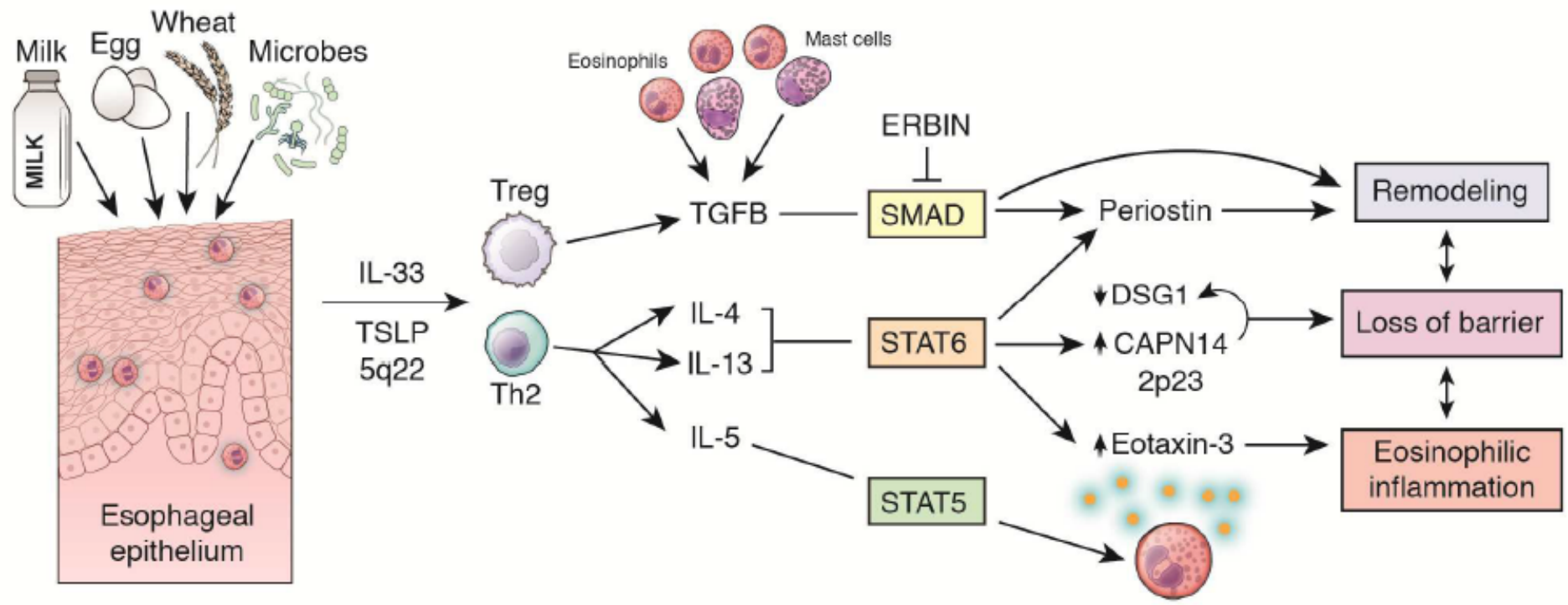


Revision of framework ongoing

- EoE will stay EoE, but likely will be formally under the EGID umbrella term
  - We will likely distinguish EoE from the non-EoE EGIDs as well
- Eosinophilic gastritis (EG) will stay the same
- Eosinophilic colitis (EC) will stay the same
- Ongoing discussion about “eosinophilic gastroenteritis”
  - Use eosinophilic gastritis and enteritis (or duodenitis) if both present
  - Redefine “eosinophilic gastroenteritis”?
  - How to best capture specific segments of small bowel involvement, with understanding that most “enteritis” is duodenitis

Non-EoE EGID pathogenesis

Let’s first talk about EoE…

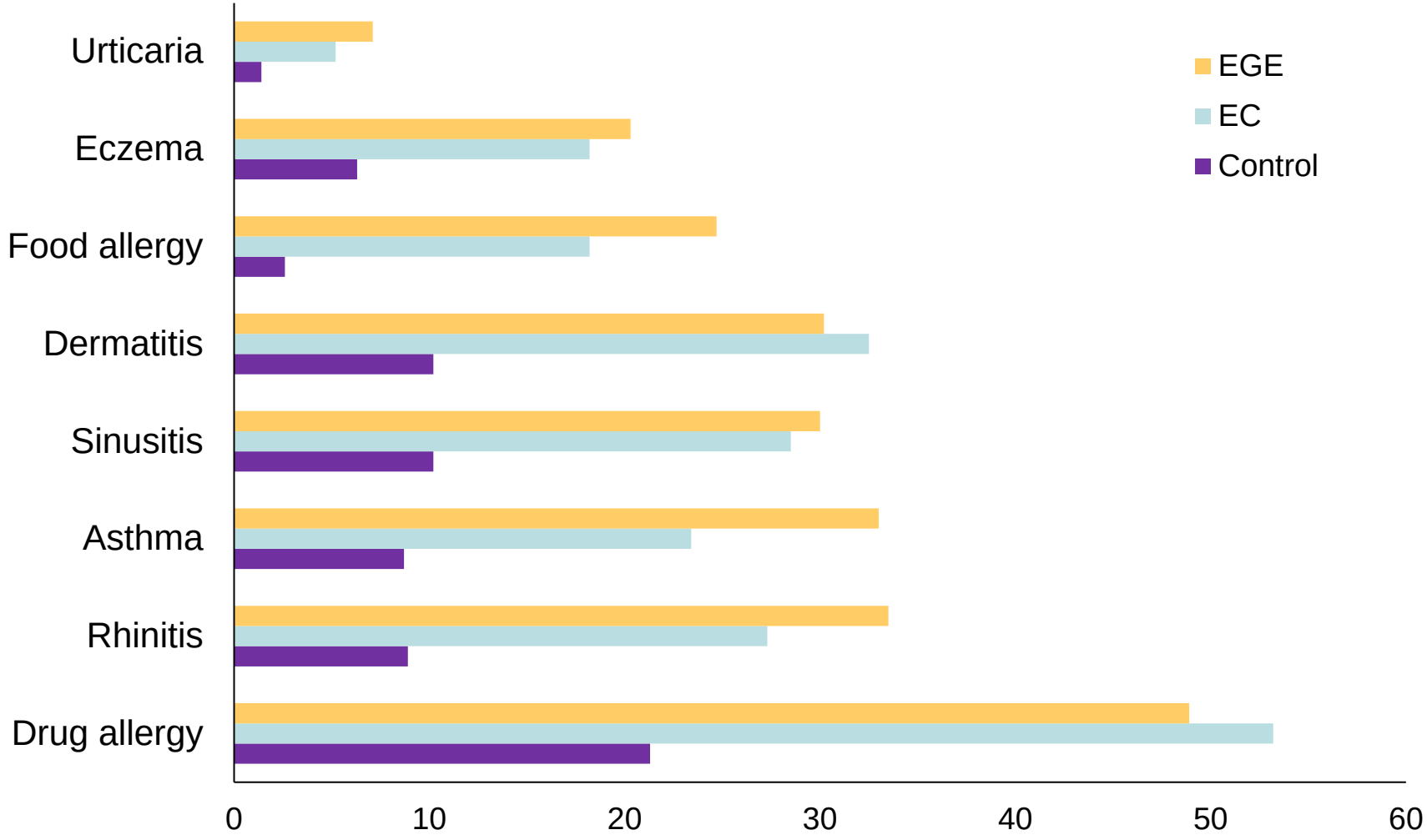


O’Shea et al, Gastroenterology, 2018

Non-EoE EGID pathogenesis

- Less investigated
- Initial data suggest that gastric and small bowel EGIDs likely share similar pathogenic features to EoE (and likely similar if it is gastric alone, gastric + small bowel, or small bowel alone)
  - Association with atopy
  - Response to elemental formula
  - Th2 type signature and cytokines
- EC pathogenesis still under investigation

Association of atopy and non-EoE EGIDs



Mansoor et al, CGH, 2017; note "EGE" from administrative coding

Association of atopy and non-EoE EGIDs

Multicenter retrospective study (CEGIR) of 376 EGID patients:

Table 2. Medical history of study population and by EGID diagnosis

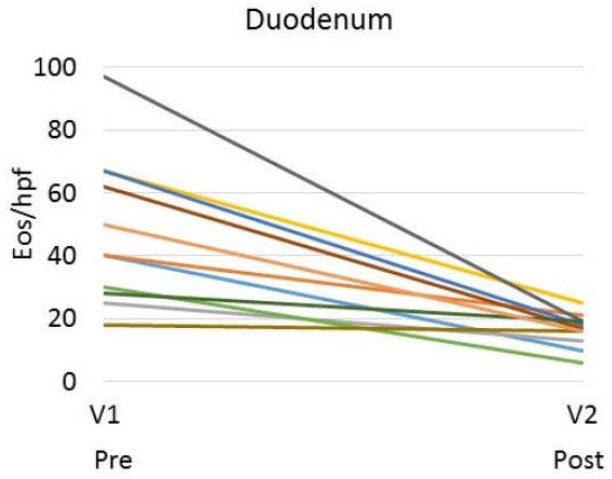
	All subjects, N = 376 (n, %)	EG, n = 142 (n, %)	EGE, n = 123 (n, %)	EC, n = 108 (n, %)	Multiple areas of eosinophilic inflammation, n = 154 (n, %)
Condition					
Any atopic condition	221 (59)	81 (57)	90 (73)	52 (48)	96 (62)
Allergic conjunctivitis	6 (2)	3 (2)	2 (2)	2 (2)	5 (3)
Allergic rhinitis	87 (23)	34 (24)	38 (31)	15 (14)	48 (31)
Angioedema	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asthma	93 (25)	38 (27)	35 (28)	24 (22)	48 (31)
Atopic dermatitis	55 (15)	18 (13)	27 (22)	11 (10)	31 (20)
Drug allergy	42 (11)	16 (11)	15 (12)	11 (10)	12 (8)
Environmental allergy	9 (2)	3 (2)	4 (3)	2 (2)	3 (33)
Food allergy	117 (31)	41 (29)	56 (46)	21 (19)	54 (46)

Pesek et al, AJG, 2019; EGE defined as stomach + small bowel or small bowel alone

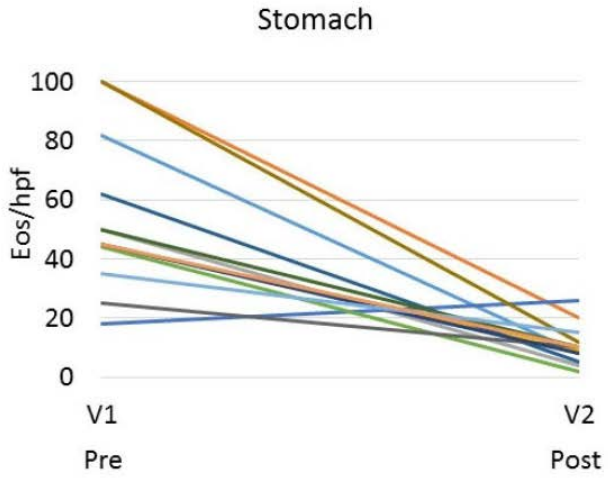
Response to elemental formula

ELEMENT study (Gonsalves et al)

- Prospective study of elemental formula x 6 wks for adults with EG/EGE
- 100% met primary outcome of histologic response (<30 eos/hpf)



40 → 16 eos/hpf; p=0.001



45 → 10 eos/hpf; p=0.002

Gonsalves et al, DDW, 2020, AB 229 (S-43); EGE=stomach and/or duodenum

Response to elemental formula

Why are these critical data?

GASTROENTEROLOGY 1995;109:1503–1512

Eosinophilic Esophagitis Attributed to Gastroesophageal Reflux: Improvement With an Amino Acid–Based Formula

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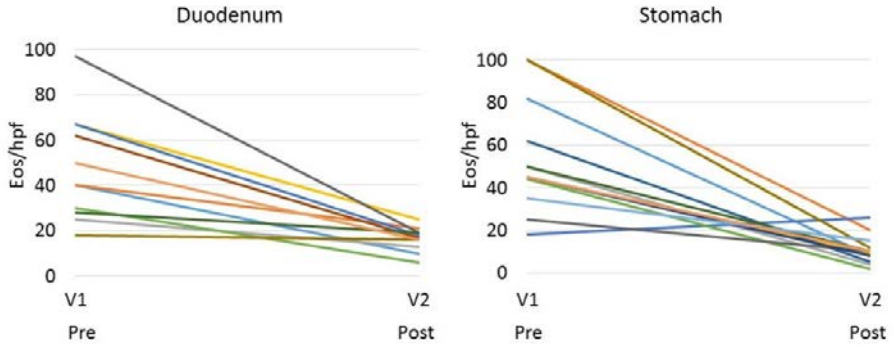
Divisions of †Pediatric Gastroenterology/Nutrition and ¶Pediatric Allergy/Immunology and Departments of *Pediatrics and ‖Pathology, The Johns Hopkins University School of Medicine, Baltimore, Maryland; and §Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama

1995: Confirmation EoE is food allergy-mediated

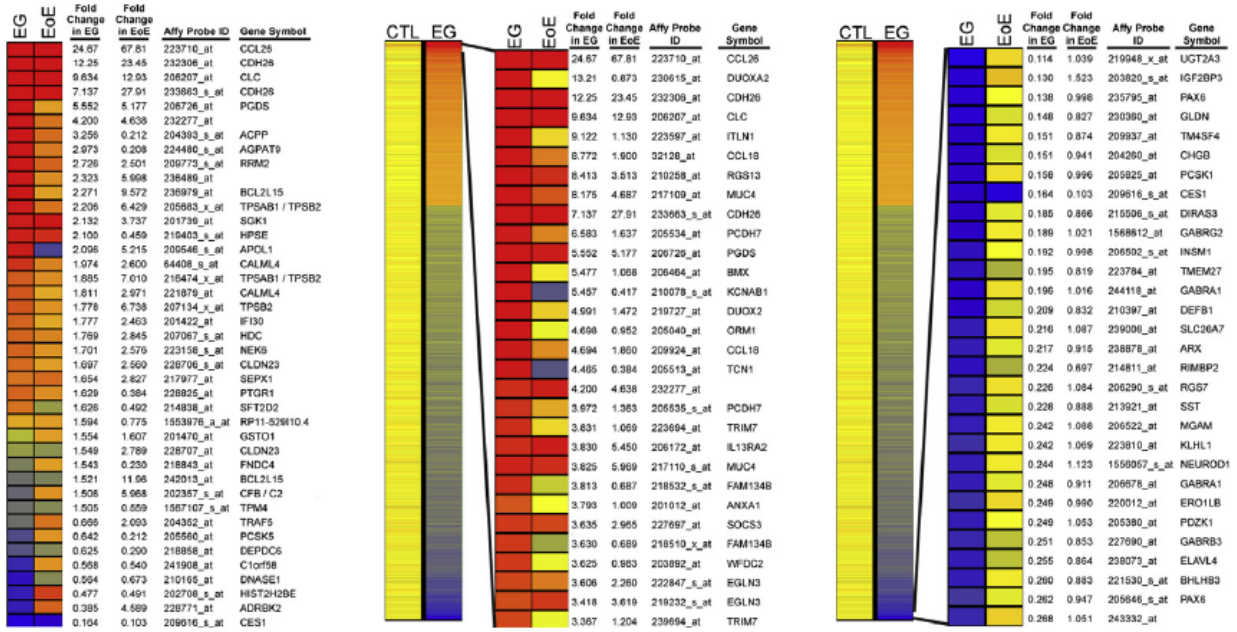


2020: Confirmation eosinophilic gastritis and/or enteritis are food allergy-mediated

EG as a Th2-mediated disease?

Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, T_H2 immunity, and a unique gastric transcriptome

Julie M. Caldwell, PhD,[a] Margaret H. Collins, MD,[b] Emily M. Stucke, BA,[a] Philip E. Putnam, MD,[c] James P. Franciosi, MD, MS, MSCE,[c]* Jonathan P. Kushner, MD,[d] J. Pablo Abonia, MD,[a] and Marc E. Rothenberg, MD, PhD[a] *Cincinnati, Ohio*

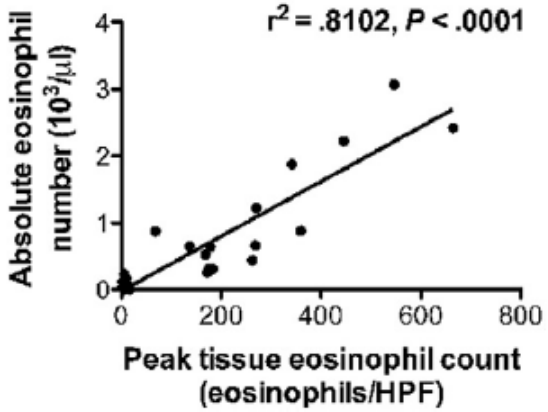


EG	EoE	Fold Change in EG	Fold Change in EoE	Affy Probe ID	Gene Symbol
		24.67	67.81	223710_at	CCL26
		12.25	23.45	232306_at	CDH26
		9.634	12.93	206207_at	CLC
		7.137	27.91	233663_s_at	CDH26
		5.552	5.177	206726_at	PGDS
		4.200	4.638	232277_at	
		3.256	0.212	204393_s_at	ACPP
		2.973	0.208	224480_s_at	AGPAT9
		2.726	2.501	209773_s_at	RRM2
		2.323	5.998	236489_at	
		2.271	9.572	236979_at	BCL2L15
		2.206	6.429	205683_x_at	TPSAB1 / TPSB2
		2.132	3.737	201739_at	SGK1
		2.100	0.459	219403_s_at	HPSE
		2.096	5.215	209546_s_at	APOL1
		1.974	2.600	64408_s_at	CALML4
		1.885	7.010	216474_x_at	TPSAB1 / TPSB2
		1.811	2.971	221879_at	CALML4
		1.778	6.738	207134_x_at	TPSB2
		1.777	2.463	201422_at	IFI30
		1.769	2.845	207067_s_at	HDC
		1.701	2.576	223158_s_at	NEK6
		1.697	2.569	228706_s_at	CLDN23
		1.654	2.827	217977_at	SEPX1
		1.629	0.384	226825_at	PTGR1
		1.626	0.492	214838_at	SFT2D2
		1.594	0.775	155397B_a_at	RP11-529I10.4
		1.554	1.607	201470_at	GSTO1
		1.549	2.789	228707_at	CLDN23
		1.543	0.230	218843_at	FNDC4
		1.521	11.06	242013_at	BCL2L15
		1.508	5.968	202357_s_at	CFB / C2
		1.505	0.559	1557107_s_at	TPM4
		0.656	2.093	204352_at	TRAF5
		0.642	0.212	205560_at	PCSK5
		0.625	0.290	218858_at	DEPDC6
		0.568	0.540	241908_at	C1orf58
		0.564	0.673	210165_at	DNASE1
		0.477	0.491	202708_s_at	HIST2H2BE
		0.395	4.589	228771_at	ADRBK2
		0.164	0.103	209616_s_at	CES1

EG	EoE	Fold Change in EG	Fold Change in EoE	Affy Probe ID	Gene Symbol
		24.67	67.81	223710_at	CCL26
		13.21	0.673	230615_at	DUOXA2
		12.25	23.45	232306_at	CDH26
		9.634	12.93	206207_at	CLC
		9.122	1.130	223597_at	ITLN1
		8.772	1.900	32126_at	CCL18
		8.413	3.513	210258_at	RGS13
		8.175	4.687	217109_at	MUC4
		7.137	27.91	233663_s_at	CDH26
		6.583	1.637	205534_at	PCDH7
		5.552	5.177	206726_at	PGDS
		5.477	1.058	206464_at	BMX
		5.457	0.417	210078_s_at	KCNAB1
		4.991	1.472	219727_at	DUOX2
		4.698	0.952	205040_at	ORM1
		4.694	1.860	209924_at	CCL18
		4.465	0.384	205513_at	TCN1
		4.200	4.638	232277_at	
		3.672	1.363	205535_s_at	PCDH7
		3.631	1.069	223694_at	TRIM7
		3.630	5.450	206172_at	IL13RA2
		3.625	5.969	217110_s_at	MUC4
		3.813	0.687	218532_s_at	FAM134B
		3.793	1.009	201012_at	ANXA1
		3.635	2.965	227697_at	SOCS3
		3.630	0.689	218510_x_at	FAM134B
		3.625	0.983	203892_at	WFDC2
		3.606	2.260	222847_s_at	EGLN3
		3.418	3.619	219232_s_at	EGLN3
		3.367	1.204	239694_at	TRIM7

EG	EoE	Fold Change in EG	Fold Change in EoE	Affy Probe ID	Gene Symbol
		0.114	1.039	219948_x_at	UGT2A3
		0.130	1.523	203820_s_at	IGF2BP3
		0.138	0.998	235795_at	PAX6
		0.148	0.827	230360_at	GLDN
		0.151	0.874	209937_at	TM4SF4
		0.151	0.941	204260_at	CHGB
		0.158	0.996	205825_at	PCSK1
		0.164	0.103	209616_s_at	CES1
		0.185	0.866	215506_s_at	DIRAS3
		0.189	1.021	1568612_at	GABRG2
		0.192	0.998	206502_s_at	INSM1
		0.195	0.819	223784_at	TMEM27
		0.196	1.016	244118_at	GABRA1
		0.209	0.832	210397_at	DEFB1
		0.216	1.087	239006_at	SLC26A7
		0.217	0.915	238878_at	ARX
		0.224	0.697	214811_at	RIMBP2
		0.226	1.084	206290_s_at	RGS7
		0.228	0.888	213921_at	SST
		0.242	1.086	206522_at	MGAM
		0.242	1.069	223810_at	KLHL1
		0.244	1.123	1556067_s_at	NEUROD1
		0.248	0.911	206578_at	GABRA1
		0.249	0.996	220012_at	ERO1LB
		0.249	1.053	205380_at	PDZK1
		0.251	0.853	227690_at	GABRB3
		0.255	0.864	238073_at	ELAVL4
		0.260	0.883	221530_s_at	BHLHB3
		0.262	0.947	205846_s_at	PAX6
		0.268	1.051	243332_at	

- Characteristic EG transcriptome
- CCL26 (eotaxin-3) most highly upregulated transcript
- IL-4, IL-5, and IL-13 were also highly upregulated or expressed

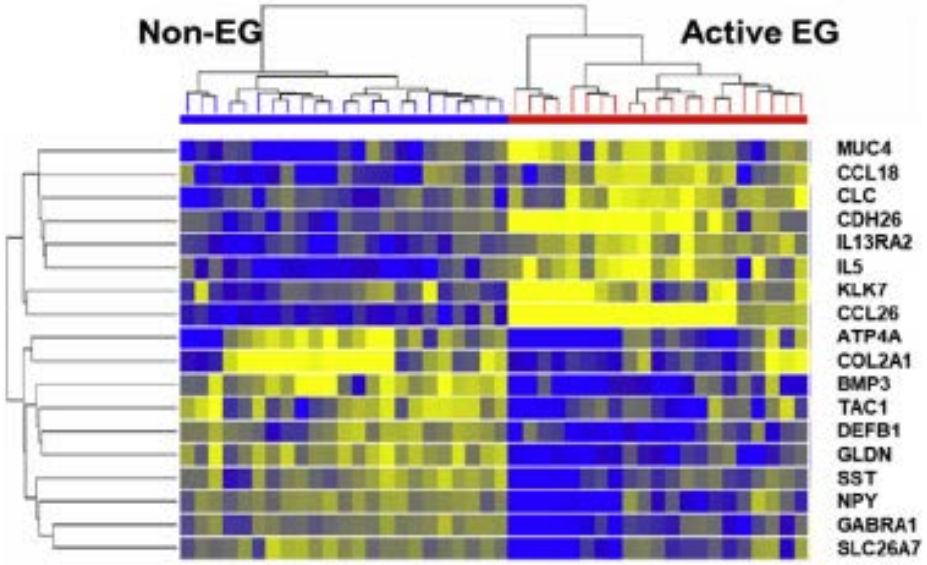


JACI, 2014

EG as a Th2-mediated disease?

Molecular, endoscopic, histologic, and circulating biomarker-based diagnosis of eosinophilic gastritis: Multi-site study

Tetsuo Shoda, MD, PhD,[a] Ting Wen, PhD,[a] Julie M. Caldwell, PhD,[a] Margaret H. Collins, MD,[b] John A. Besse, BS,[a] Garrett A. Osswald, BS,[a] J. Pablo Abonia, MD,[a] Nicoleta C. Arva, MD, PhD,[c] Dan Atkins, MD,[d] Kelley E. Capocelli, MD,[e] Evan S. Dellon, MD, MPH,[f] Gary W. Falk, MD, MS,[g] Nirmala Gonsalves, MD,[h] Sandeep K. Gupta, MD,[i] Ikuo Hirano, MD,[h] Vincent A. Mukkada, MD,[j] Philip E. Putnam, MD,[j] Rachel M. Sheridan, MD,[b] Amanda K. Rudman Spergel, MD,[k] Jonathan M. Spergel, MD, PhD,[l] Joshua B. Wechsler, MD, PhD,[m] Guang-Yu Yang, MD, PhD,[n] Seema S. Aceves, MD, PhD,[o] Glenn T. Furuta, MD,[p] and Marc E. Rothenberg, MD, PhD,[a] on behalf of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)* *Cincinnati, Ohio, Evanston, Chicago, and Peoria, Ill, Aurora, Colo, Chapel Hill, NC, Philadelphia, Pa, Bethesda, Md, and San Diego, Calif*



Shoda et al (CEGIR), JACI, 2020

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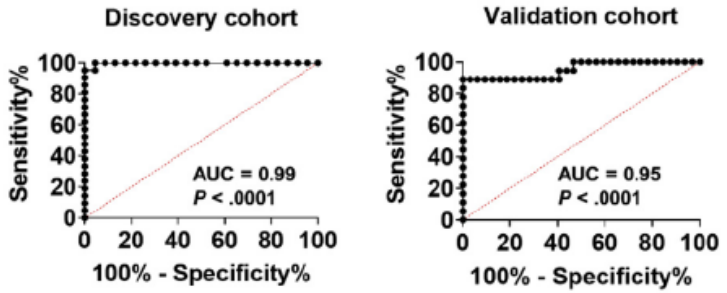

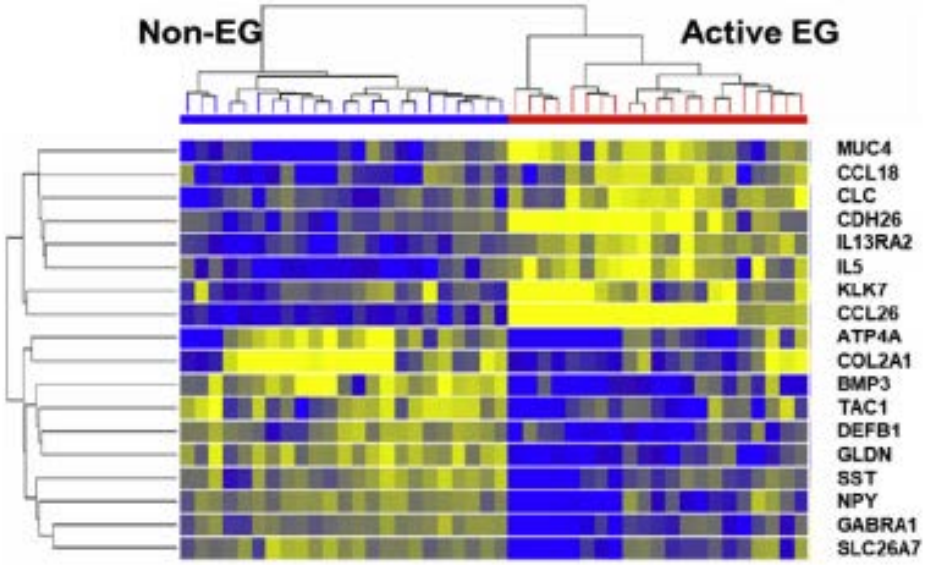

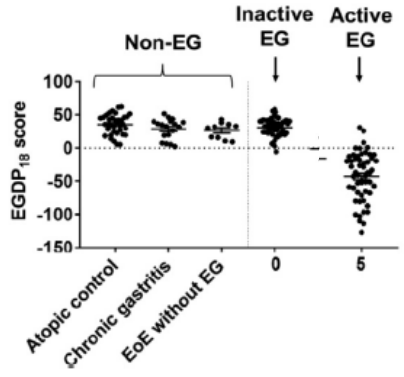

Shoda et al (CEGIR), JACI, 2020

EG as a Th2-mediated disease?

Molecular, endoscopic, histologic, and circulating biomarker-based diagnosis of eosinophilic gastritis: Multi-site study

Tetsuo Shoda, MD, PhD,[a] Ting Wen, PhD,[a] Julie M. Caldwell, PhD,[a] Margaret H. Collins, MD,[b] John A. Besse, BS,[a] Garrett A. Osswald, BS,[a] J. Pablo Abonia, MD,[a] Nicoleta C. Arva, MD, PhD,[c] Dan Atkins, MD,[d] Kelley E. Capocelli, MD,[e] Evan S. Dellon, MD, MPH,[f] Gary W. Falk, MD, MS,[g] Nirmala Gonsalves, MD,[h] Sandeep K. Gupta, MD,[i] Ikuo Hirano, MD,[h] Vincent A. Mukkada, MD,[j] Philip E. Putnam, MD,[j] Rachel M. Sheridan, MD,[b] Amanda K. Rudman Spergel, MD,[k] Jonathan M. Spergel, MD, PhD,[l] Joshua B. Wechsler, MD, PhD,[m] Guang-Yu Yang, MD, PhD,[n] Seema S. Aceves, MD, PhD,[o] Glenn T. Furuta, MD,[p] and Marc E. Rothenberg, MD, PhD,[a] on behalf of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)*
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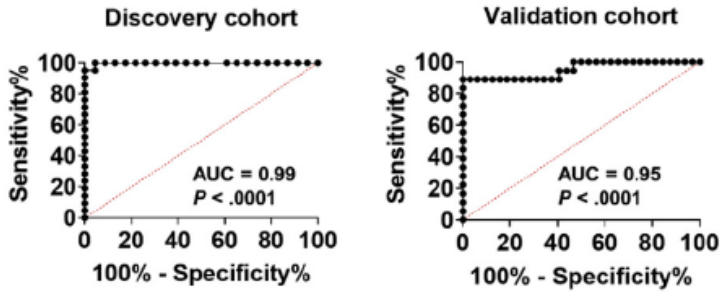

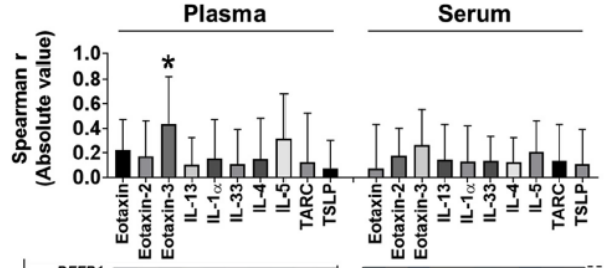

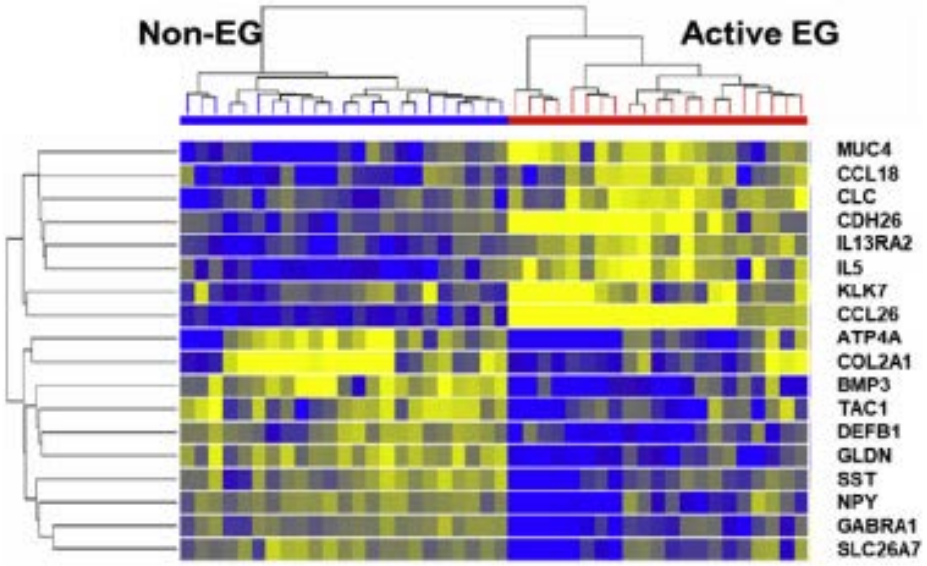

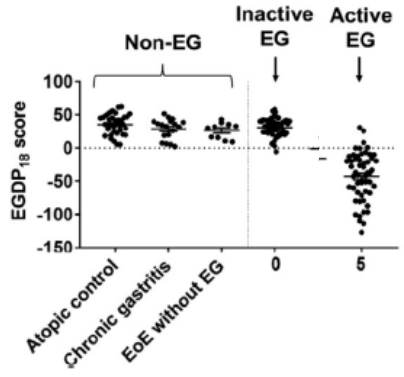

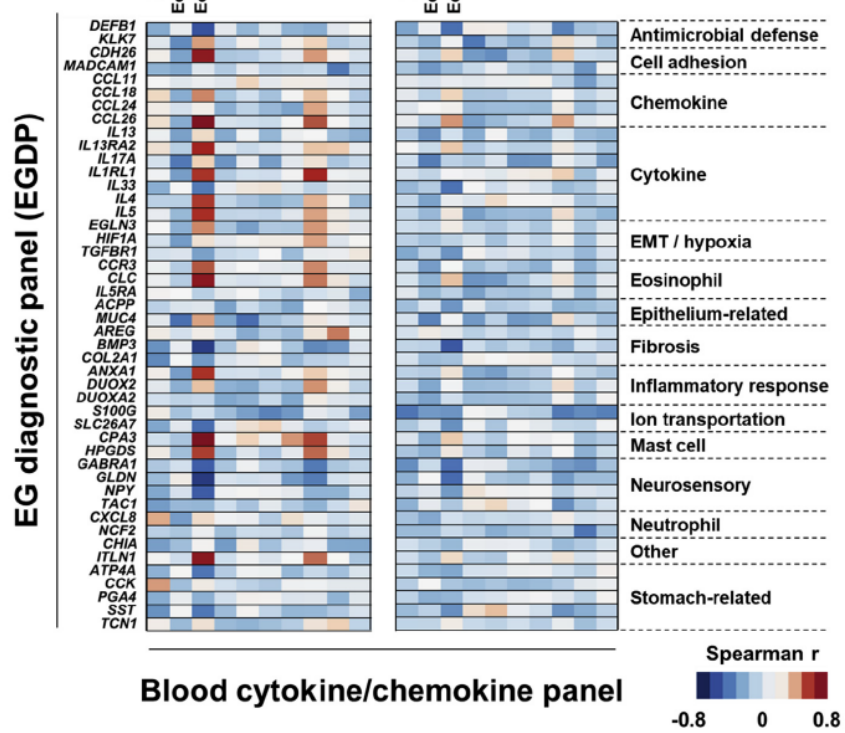

Shoda et al (CEGIR), JACI, 2020

Response by areas of involvement?

- Prospective study of elemental formula for treatment of EG +/- enteritis*
  - All patients responded to treatment similarly regardless of gastric, duodenal, or both gastric and duodenal involvement
- Randomized trial of a biologic for treatment of EG +/- EoD**
  - All patients responded to treatment similarly regardless of gastric, duodenal, or both gastric and duodenal involvement
- Suggests that EG with or without EoD, and EoD alone, may respond in the same way to treatment, and could share underlying pathogenesis
  - Needs to be confirmed in future studies
  - Work is ongoing with transcriptome data

*Gonsalves et al, DDW, 2019; **Dellon et al, NEJM, 2020

Pathogenesis and future treatment targets

Some similar Th2 pathway treatment targets for EG as for EoE

- IL-4, IL-5, IL-13
- TSLP
- Eotaxin-3

Potential for biomarkers?

Emerging data to come for duodenitis/enteritis and colitis…

Pathogenesis and outcomes

- Symptoms and pathologically elevated eosinophils are important parts of disease activity → natural to consider these as endpoints
- But how to approach histologic endpoints when a cell type is normally in a tissue?
- Consideration of other endpoints (looking forward to our discussions today!)
  - Histologic severity (not just a cell count)
  - Molecular activity (“EGDP”)
  - Clinical complications
  - Endpoints to allow/encourage novel drug mechanisms
  - Many other options!

Summary

- Non-EoE EGIDs are characterized clinically by GI symptoms and histologically by pathologically increased eosinophilic inflammation
  - Rare diseases that are likely under recognized; prevalence increasing
- Updated nomenclature coming soon
- Understanding of pathogenesis rapidly increasing
  - Demonstration that EG is a Th2-mediated disease
  - Implications for diagnosis, monitoring/biomarkers, and treatment targets
  - Implications for thinking about outcomes
  - Data to emerge for eosinophilic duodenitis/enteritis

Thank you!

Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI): Eosinophilic Gastrointestinal Disorders Beyond EoE

Margaret H. Collins, M.D.
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University of Cincinnati
Cincinnati Children's Hospital Medical Center
Cincinnati, OH

July 21, 2021

DISCLOSURES

- **Margaret H Collins** has received research funding from Meritage Pharma Inc., Receptos/Celgene, Regeneron and Shire, a Takeda company, and is a consultant for Allakos, Arena Pharmaceuticals, AstraZeneca, Calypso, EsoCap Biotech, GlaxoSmithKline, Receptos/Celgene/BMS, Regeneron, Alimentiv (formerly Robarts Clinical Trials, Inc) and Shire, a Takeda company.

EOSINOPHILIC GASTROINTESTINAL DISORDERS (EGID)

- EGID are clinicopathologic diagnoses.
- Symptoms are consistent with the affected part of the GI tract.
- The pathologic portion of the diagnosis includes excess eosinophils in GI mucosal biopsies.
- Threshold values to identify excess eosinophils can be helpful but lead to oversimplification.
- In addition to excess eosinophils, abnormalities in structures comprising the mucosa are found.

REPORTED PEAK EOSINOPHIL COUNTS IN THE UPPER GI TRACT

Site	#/0.27 mm^2	References
Antrum	<1-19	1, 2, 3
Corpus/fundus	<1-16	1, 2, 3
Stomach NOS	3-33	4, 5, 6, 7
Duodenal bulb	Not reported	
Duodenum	<1-70	1, 2, 3, 4, 7, 8, 9, 10

1-Silva et al Virchows Arch 2018;473:313 2-Debrosse et al Pediatr Develop Pathol 2006;9:210 3-Chernetsova et al 2016;54:55 4-Reed et al Clin Gastroenterol Hepatol 2021; doi: 10.1016 5-Lwin et al Mod Pathol 2011;24:556 6-Caldwell et al J Clin Immunol 2014;134:1114 7-Koutri et al Ann Gastroenterol 2020;33:508 8-Lowichik and Weinberg 1996;9:110 9-Challacombe et al J Pediatr Nutr 1986:5:887 10 Maluenda et al J Pediatr Nutr 1984;3:349

REPORTED PEAK EOSINOPHIL COUNTS IN THE LOWER GI TRACT

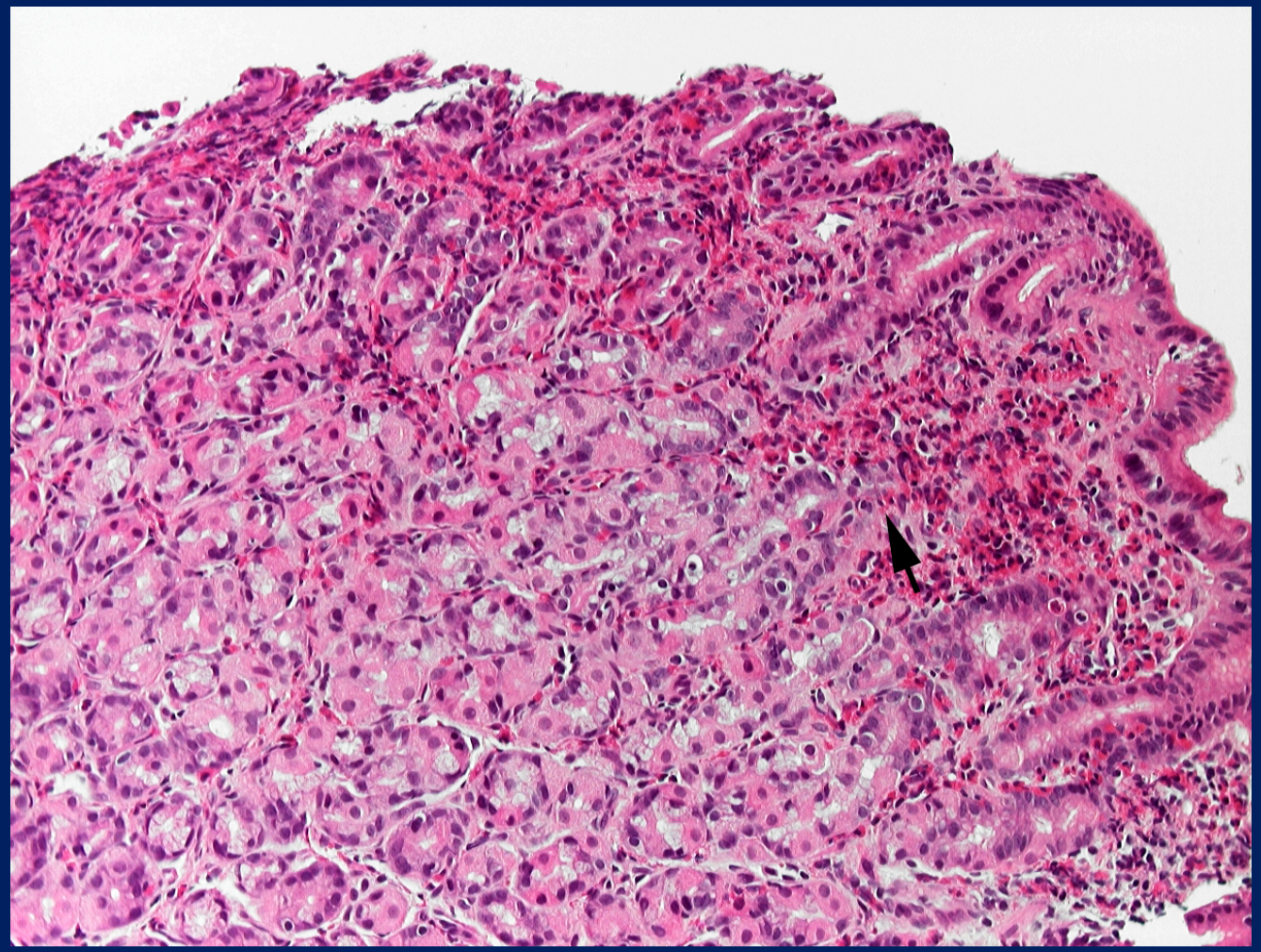
Site	#/0.27mm^2	Reference
Ileum	<1-92	1, 2, 3, 7
Cecum	<1-46	1, 3, 11, 7
Ascending colon	<1-48	1, 2, 3, 7, 11
Transverse colon	1-41	1, 2, 3, 7, 11
Descending colon	<1-25	1, 7, 11
Sigmoid	0-24	1, 3, 7
Rectum	0-31	1, 2, 3, 7

1-Silva et al Virchows Arch 2018;473:313 2-Debrosse et al Pediatr Develop Pathol 2006;9:210 3-Chernetsova et al 2016;54:55 7-Koutri et al Ann Gastroenterol 2020;33:508 11 Saad Pediatr Develop Pathol 2011;14:294

EOSINOPHILIC GASTRITIS (EG)

- Threshold values of eosinophilic inflammation for the pathologic portion of an EG diagnosis utilized in some studies include
  - 30 or more eosinophils in 5 or more high power fields (hpf) in children and adults
    - Mod Pathol 2011;24:556-563
    - J Allergy Clin Immunol 2014;134:1114-1124
    - J Allergy Clin Immunol 2020;145:255-269
  - 70 or more eosinophils in 3 or more hpf in children
    - Am J Gastroenterol 2014;109:1277-1285

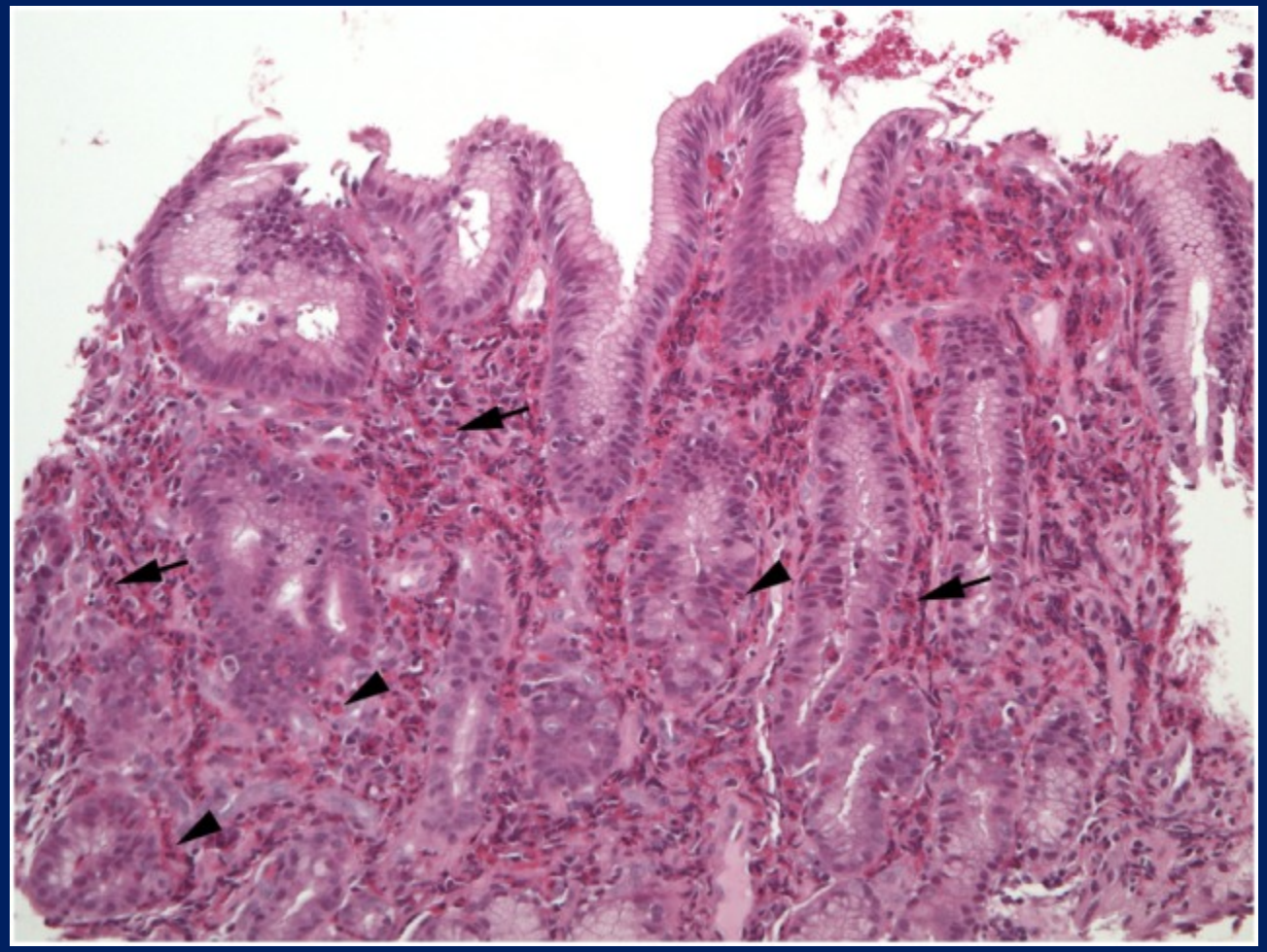
EG



Large numbers of eosinophils in lamina propria, and numerous intraepithelial eosinophils (arrow)

Gastrointest Endoscopy Clin N Am 2008;18:59-71

EG



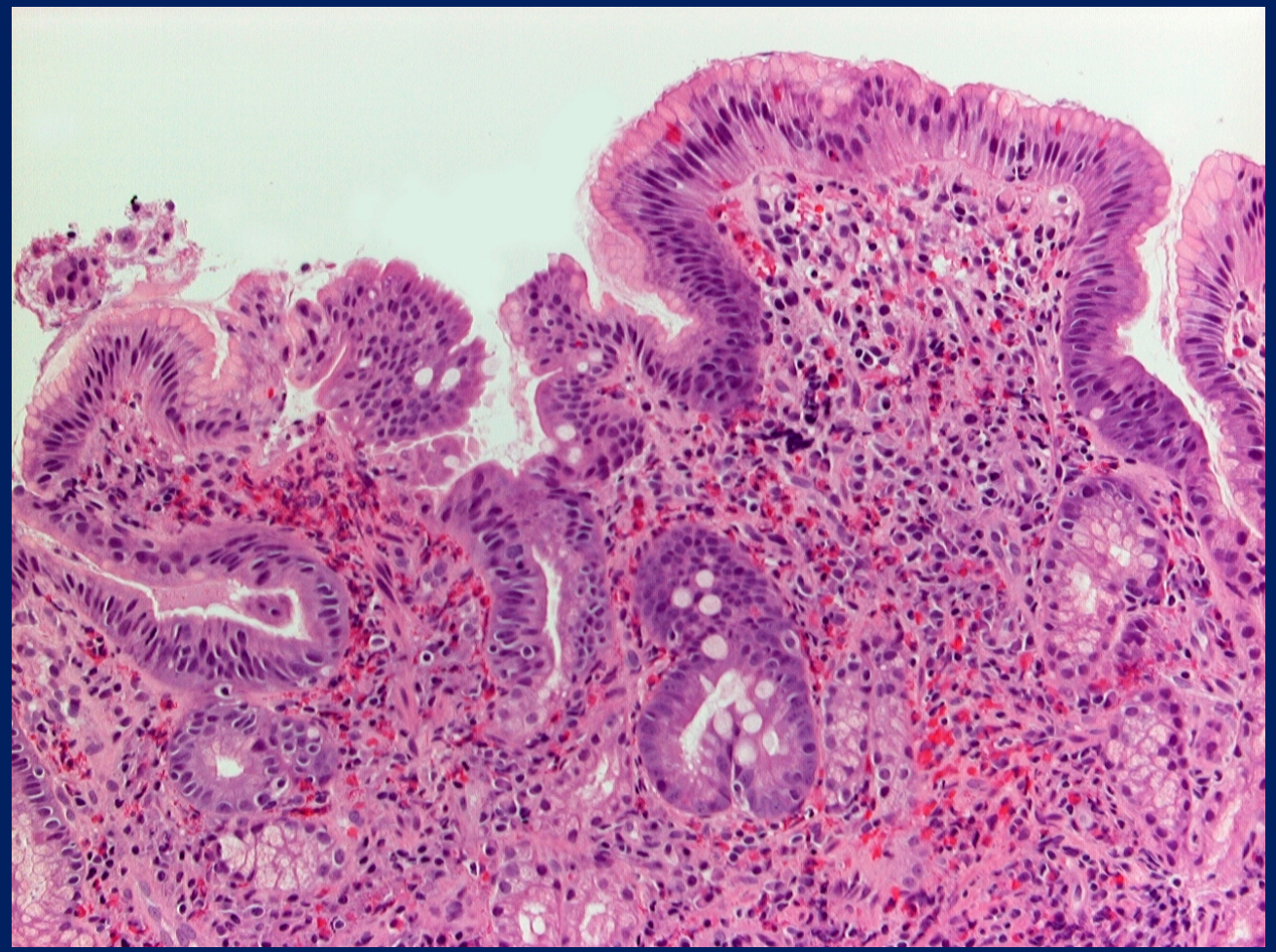
Almost total loss of mucin from reactive epithelial cells with significant architectural glandular abnormalities in addition to numerous lamina propria eosinophils

FrontMed (Lausanne) 2018;4:271

EOSINOPHILIC DUODENITIS (EoD)

- A threshold eosinophil value could be 2x the normal peak value of 26/hpf = >52/hpf.
- One study used a threshold value of 30 eosinophils in 3 hpf for the pathologic part of the diagnosis of EoD.
  - New Engl J Med 2020;383:1624-1634

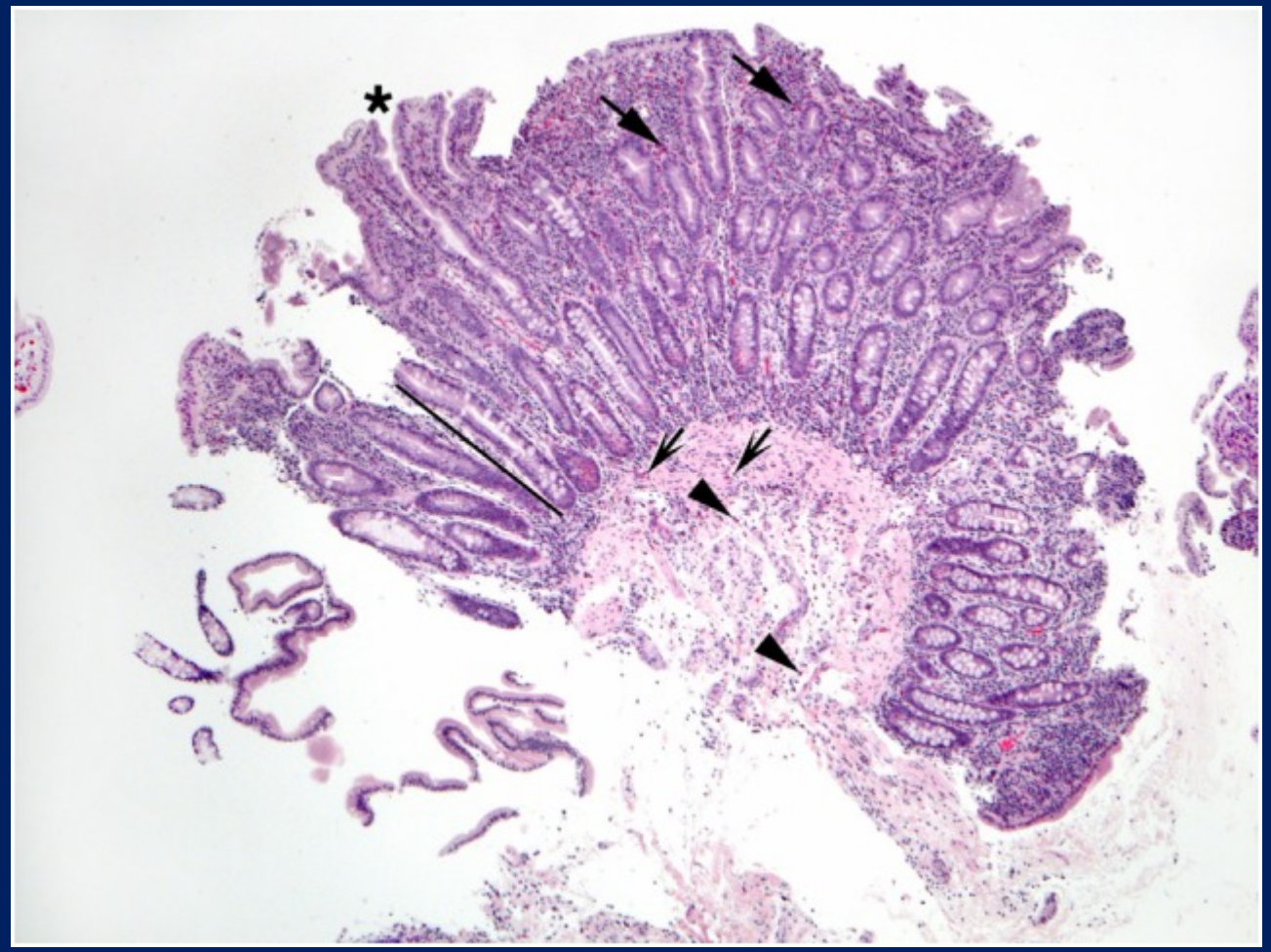
EoD



Foveolar metaplasia at surface that is almost avillous with numerous lamina propria eosinophils.

Gastrointest Endoscopy Clin N Am 2008;18:59-71

EoD



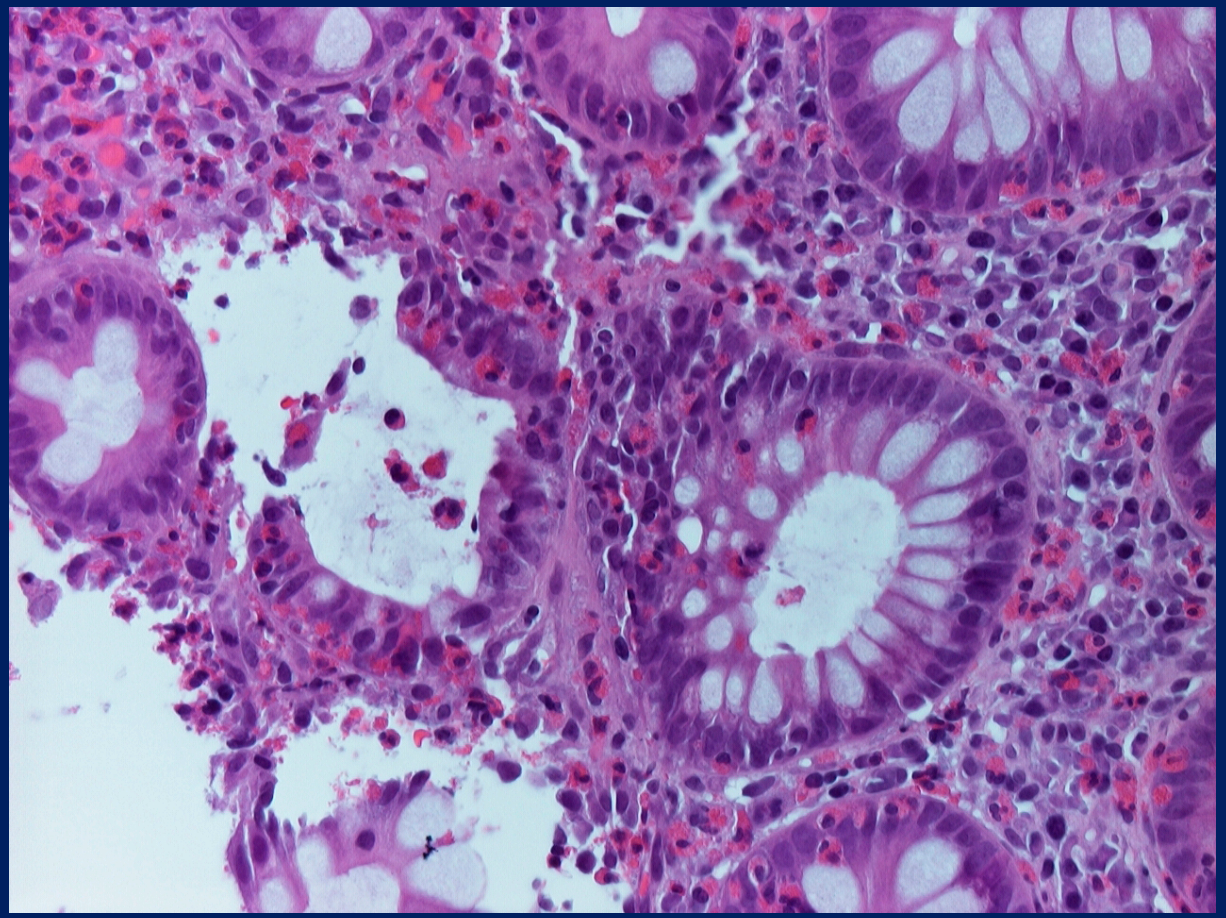
Crypt hyperplastic villous atrophy with numerous eosinophils in the lamina propria (arrows), in the muscularis mucosa (white edge arrows), and the submucosa (arrowheads). Few villiform areas remain (asterisk).

FrontMed (Lausanne) 2018;4:271

EOSINOPHILIC COLITIS (EC)

- Threshold values are the most complicated in the GI tract because the density of eosinophils normally varies in the colon, the greatest density occurring in the right colon and the least in the sigmoid/rectum.
- Excess eosinophils could be considered a multiple of the peak count/hpf in normal biopsies, including 2 × 50/hpf or 100/hpf in cecum and ascending colon, 2 × 42/hpf or 84/hpf in transverse and descending colon, and 2 × 32/hpf or 64/hpf in rectosigmoid mucosa
  - Pediatr Surg Int 2021;37:485-490

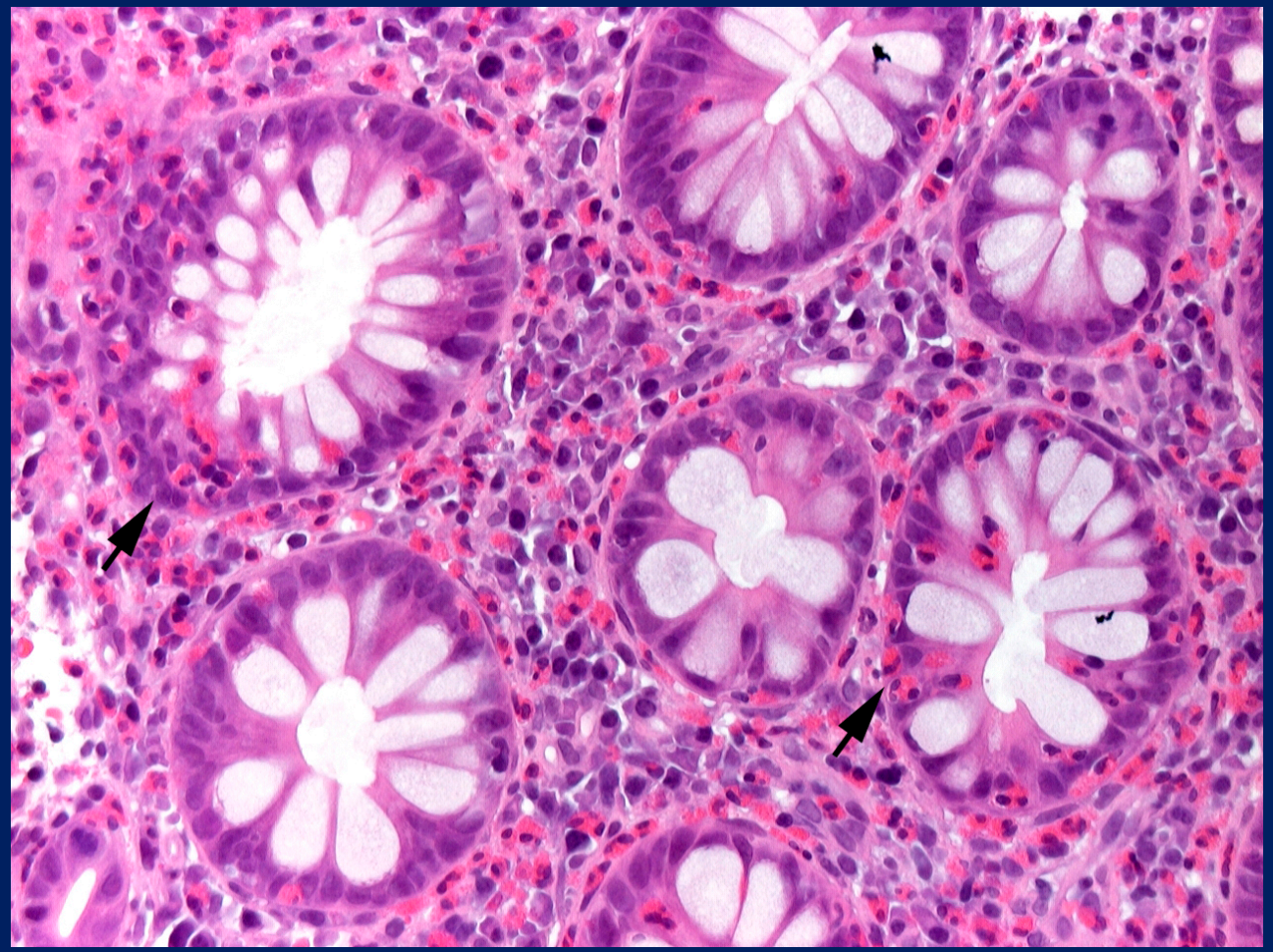
EC



Numerous eosinophils in lamina propria and crypt epithelium

Gastrointest Endoscopy Clin N Am 2008;18:59-71

EC



Numerous eosinophils in lamina propria and crypt epithelium (arrow)

Gastrointest Endoscopy Clin N Am 2008;18:59-71

CONCLUSIONS

- Threshold values for non-EoE EGID are not currently defined/widely accepted (in contrast to 15 eosinophils/hpf for EoE).
- Significant changes other than eosinophil inflammation that are found in biopsies showing abnormal concentrations of eosinophils likely are related to the eosinophil inflammation.

Clinical Symptoms/Signs and Natural History of non-EoE EGIDS

GREAT IV Meeting

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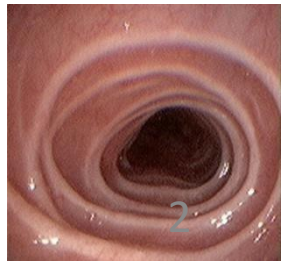
July 21, 2021

Northwestern Medicine®

Disclosures

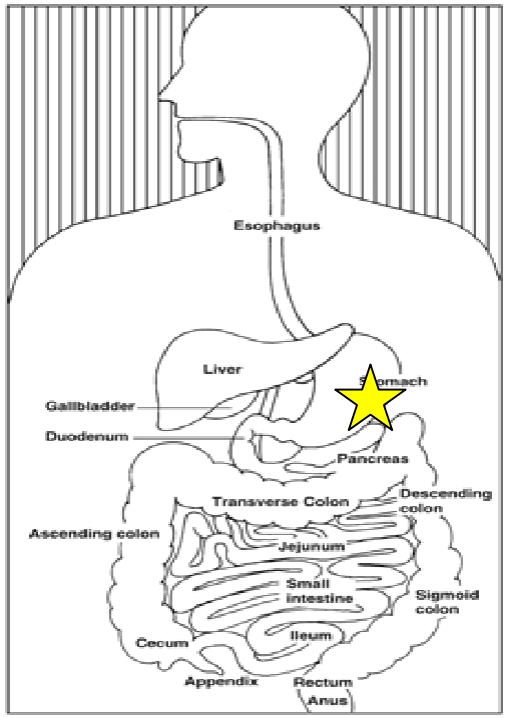
- Up-to-Date Chapter Author
- Consultant: Allakos, Sanofi-Regeneron, Astra-Zeneca, Abbvie, Nutricia
- Discussing off-label use of medications for EGID
- CEGIR (U54 AI117804)
  - Rare Disease Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), NCATS, and is funded through collaboration between NIAID, NIDDK, and NCATS.



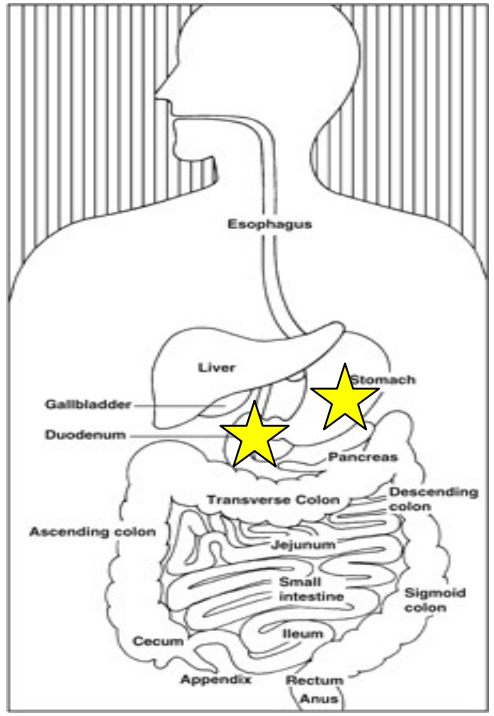
Eosinophilic Gastrointestinal Disease: *Overview*

- Clinical Presentation
- Endoscopic Features
- Impact on Quality of Life
- Natural History and Disease Course

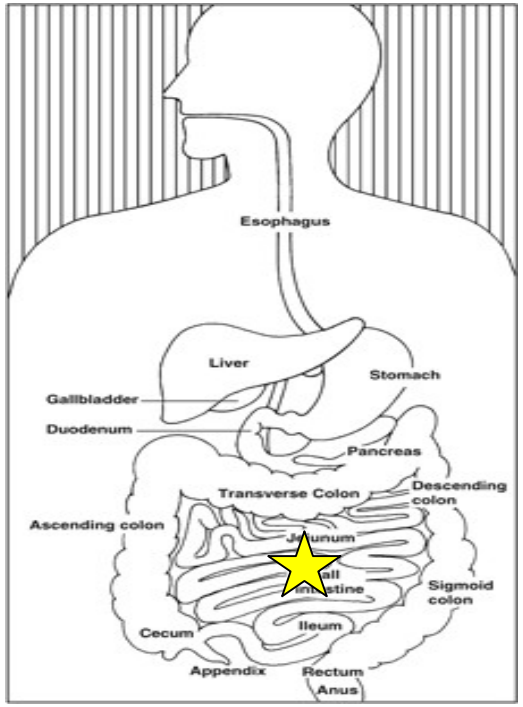
What is Eosinophilic Gastrointestinal Disease?



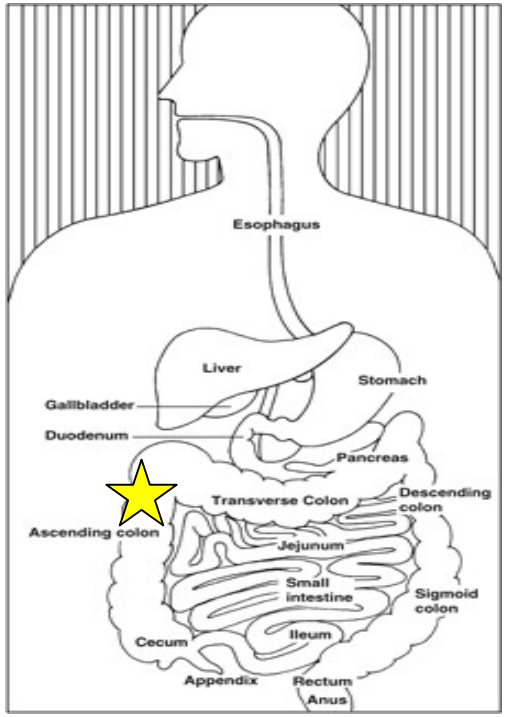
Eosinophilic Gastritis



Eosinophilic Gastroenteritis



Eosinophilic Enteritis



Eosinophilic Colitis

Eosinophilic Gastrointestinal Disease:
Clinical Presentation May Differ

- Symptoms determined by organ AND layer of bowel wall involved
  - Mucosal Variant
  - Muscular Variant
  - Serosal Variant

Symptoms Vary by Organ Involvement

	Eosinophilic gastritis
Clinical Symptoms	Abdominal Pain, Nausea, Vomiting, Early Satiety +/- Diarrhea
Lab Testing	Anemia, Peripheral Eos, Low Protein, Low Iron
Imaging	+/- gastric thickening, pyloric stenosis
Atopy	+

Symptoms Vary by Organ Involvement

	Eosinophilic gastritis	**Eosinophilic gastroenteritis** *(involvement of gastric and small bowel)*
Clinical Symptoms	Abdominal Pain, Nausea, Vomiting, Early Satiety +/- Diarrhea	Abdominal Pain, Nausea, Vomiting, Early Satiety, Diarrhea, Bloating
Lab Testing	Anemia, Peripheral Eos, Low Protein, Low Iron	Anemia, Peripheral Eos, Low Protein, Low Iron
Imaging	+/- gastric thickening, pyloric stenosis	+/- Small bowel thickening or strictures
Atopy	+	+

Symptoms Vary by Organ Involvement

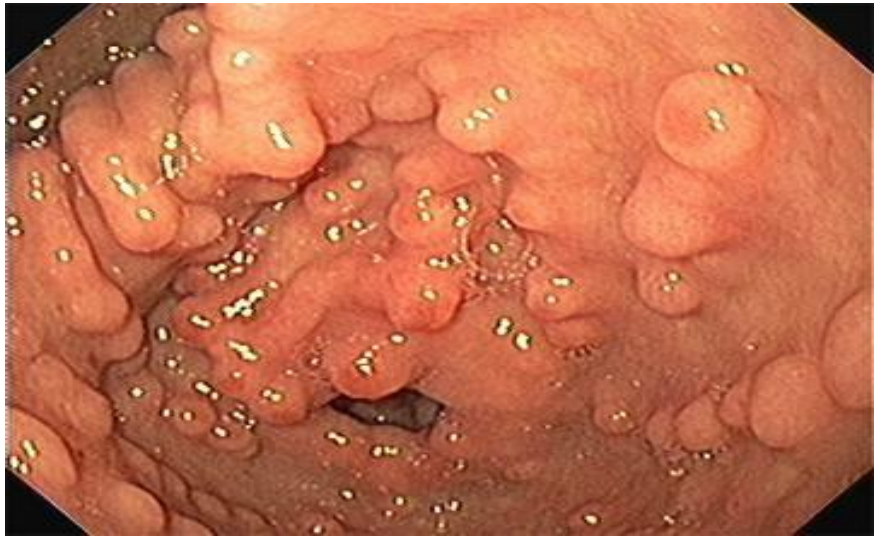
	Eosinophilic gastritis	**Eosinophilic gastroenteritis** *(involvement of gastric and small bowel)*	**Eosinophilic colitis**
Clinical Symptoms	Abdominal Pain, Nausea, Vomiting, Early Satiety +/- Diarrhea	Abdominal Pain, Nausea, Vomiting, Early Satiety, Diarrhea, Bloating	Abdominal pain, Diarrhea, Rectal Bleeding
Lab Testing	Anemia, Peripheral Eos, Low Protein, Low Iron	Anemia, Peripheral Eos, Low Protein, Low Iron	Anemia, Peripheral Eos
Imaging	+/- gastric thickening, pyloric stenosis	+/- Small bowel thickening or strictures	+/- colonic thickening
Atopy	+	+	+/-

Symptoms Vary by Tissue Layer Involvement

Mucosal Variant	Muscular Variant	Serosal Variant
• Most common type • Decreased appetite, early satiety, nausea, vomiting, abdominal pain • Diffuse small bowel disease: malabsorption, failure to thrive, protein-losing enteropathy	• Wall thickening, impaired motility, rigidity • Symptoms of intestinal obstruction (eg, nausea, vomiting, abdominal distention, gastric outlet obstruction)	• Least common type • Usually w/ enteritis • Isolated ascites or in combination with symptoms of mucosal or muscular EGE • Eosinophilic predominant ascites

Gonsalves N. *Clin Rev Allergy Immunol*. 2019.

EGID:
Mucosal Disease

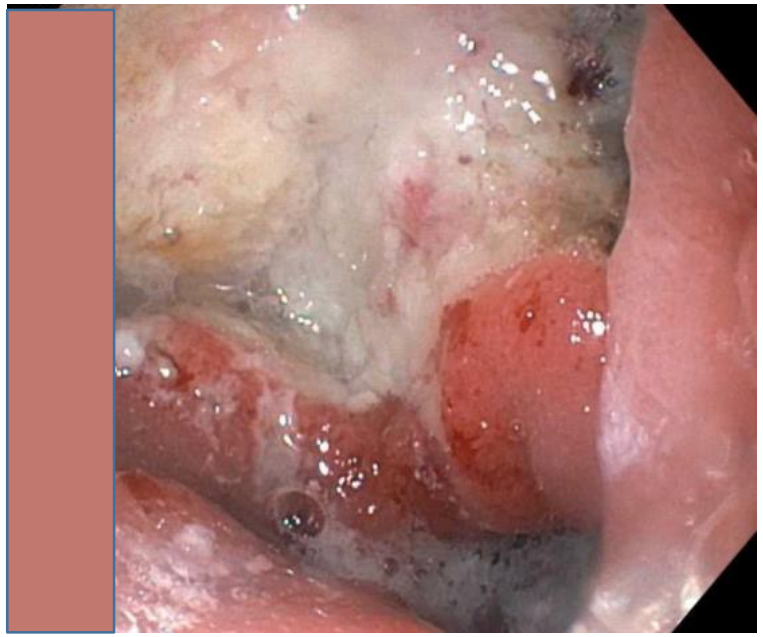


- 28 yo male with nausea/vomiting/diarrhea 30lb wt loss
- Labwork with albumin 3.0, absolute eosinophils 2200
- EGD/Colon with polypoid lesions in antrum and ileum
- Dx: EGID
- Mucosal Form
  - Stomach
  - Ileum

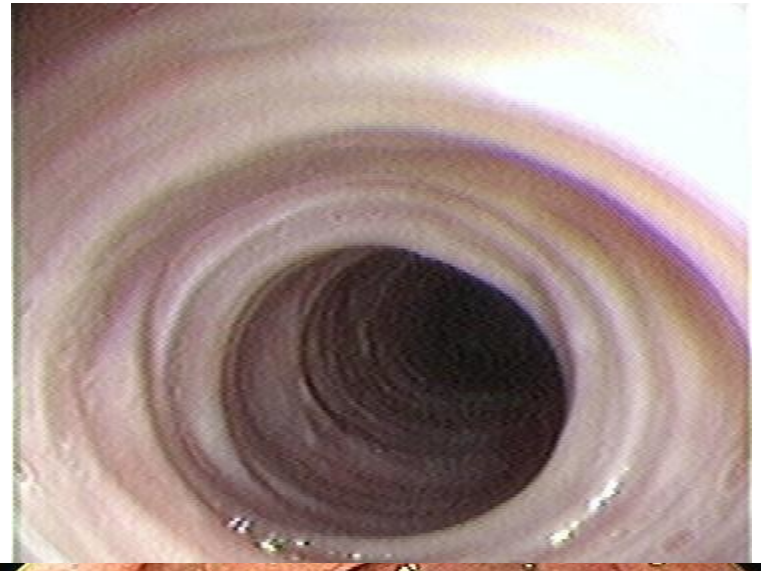
Clinical Case

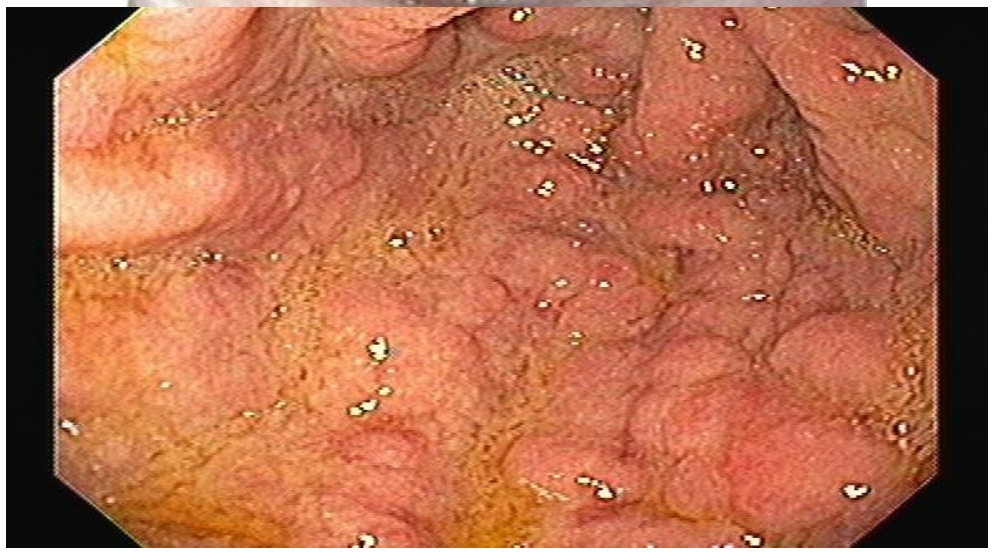
- 24 yo female with progressive n/v/d, early satiety, bloating and weight loss
- Refractory nonhealing duodenal bulb ulcer for over a year
- Repeat endoscopy post ppi and steroids with persistent ulcer and duodenal edema/early
- stenosis and >100 eosinophils in duodenum and stomach

DX: EGID- Mucosal & Muscular Stomach and Duodenum



EGID:
Muscular Disease

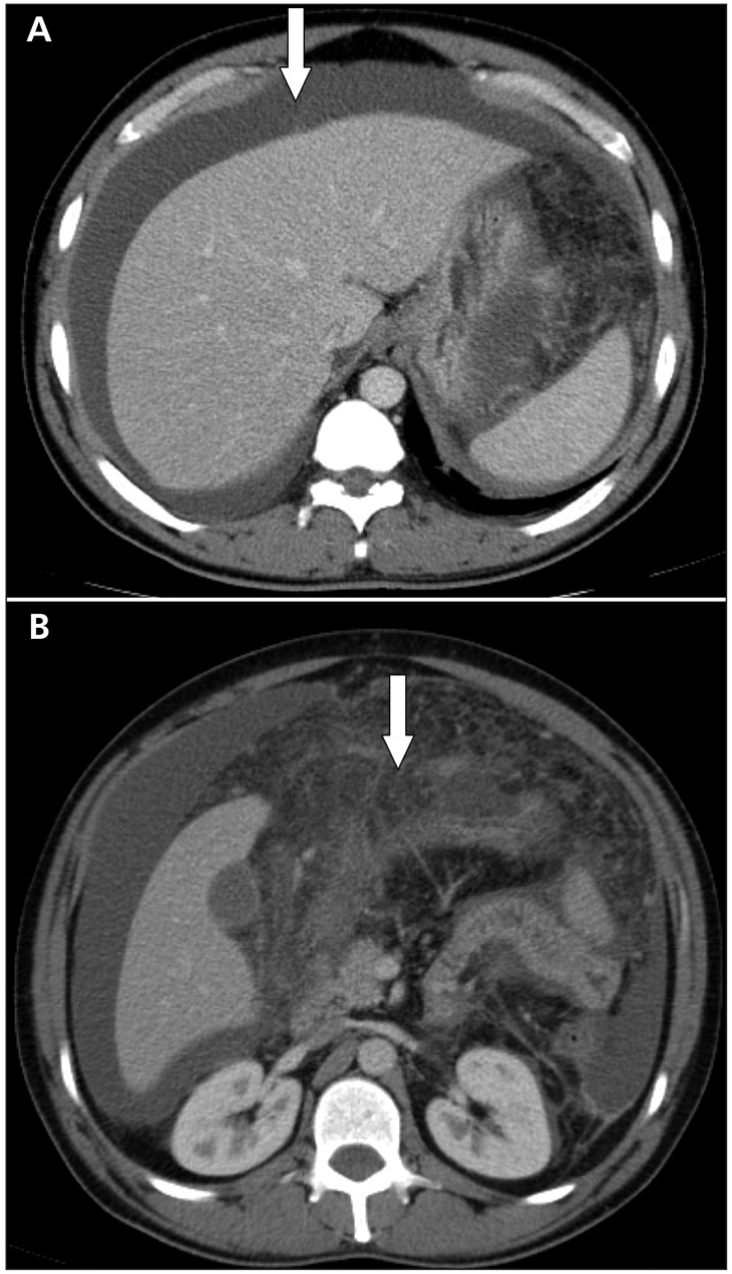




- 48 yo male with lifelong dysphagia who presents with chronic abdominal pain and nonhealing duodenal ulcers with recurrent gi bleeding
- Atopic, eosinophils 1200, alb 3.2
- Endoscopy with EGID
  - Esophagus
  - Stomach
  - Duodenum
- Mucosal and muscular variant (significant duodenal stricturing)

EGID: *Serosal Disease*

- 65 yo male with abdominal pain and diarrhea presents with abdominal distension
- Hx of asthma
- CT imaging with significant ascites
  - 88% eosinophils
  - Absolute count in blood was 8000
- Underwent hematology workup and ruled out for HES



CMAJ January 11, 2011 183 (1) E65-E67

Distinguishing EGID from other disorders

Diagnostic Criteria for EoE

EoE is a **chronic** immune-mediated **clinico-pathologic** disease

Diagnostic Criteria for Non-EoE EGID- *coming soon!*

Non-Eoe Egids are **chronic** immune-mediated **clinico-pathologic** diseases

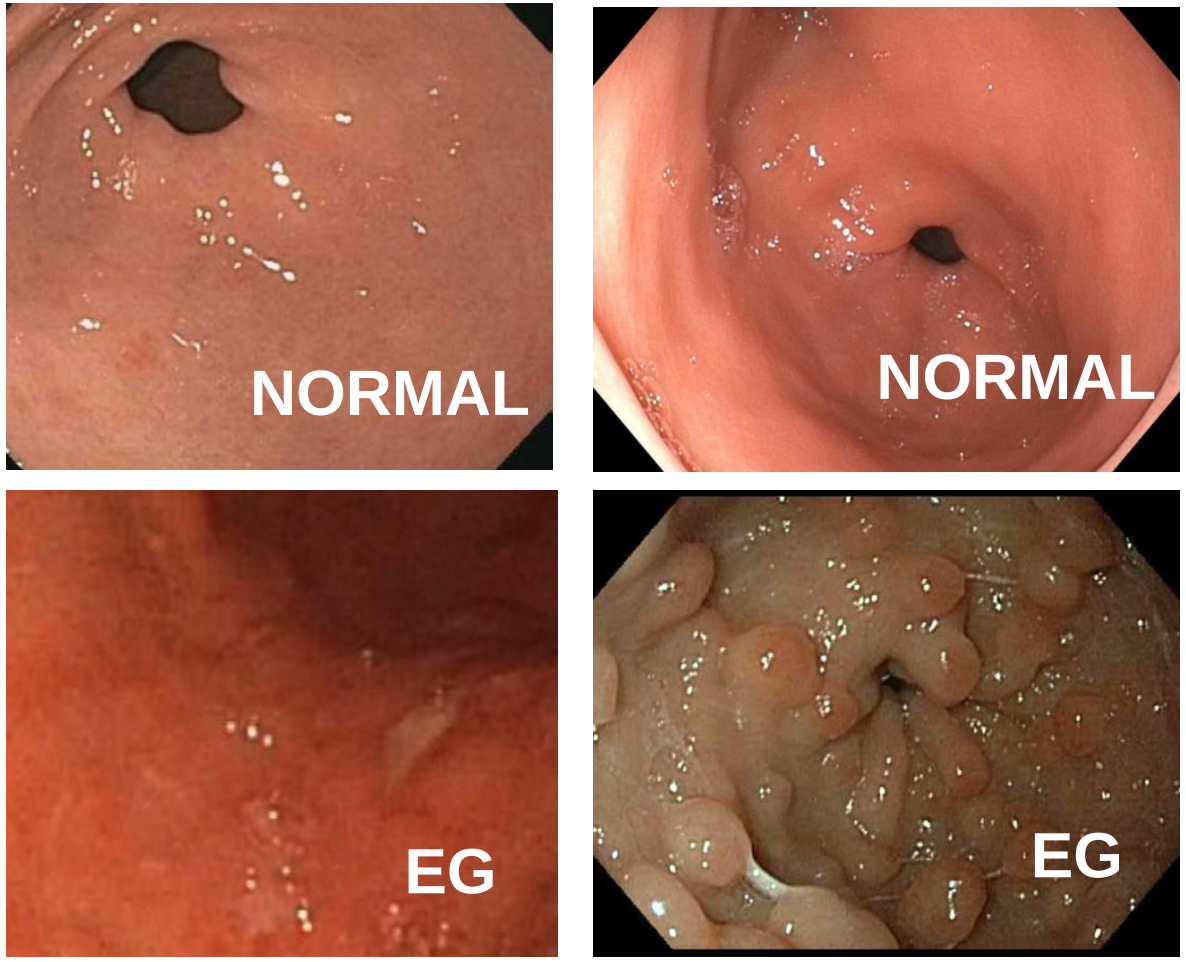
"When you see it you know it" – Margaret Collins

Eosinophilic Gastrointestinal Disease: *Overview*

- Clinical Presentation
- Endoscopic Features
- Impact on Quality of Life
- Natural History and Disease Course

Endoscopic Features

Eosinophilic Gastritis Endoscopic Reference System (EG-REFFS)

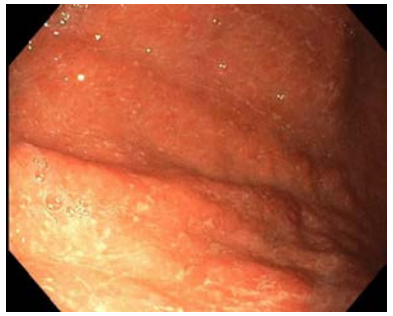
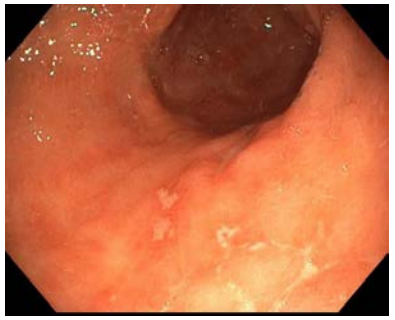
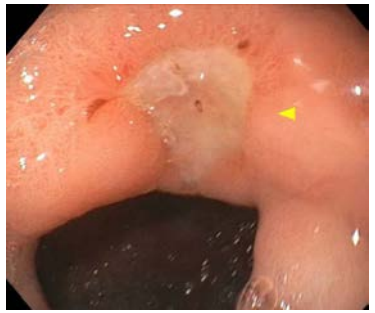


- **Erosion/Ulceration**
- **Granularity**
- **Raised lesion/nodule**
- **Erythema**
- Thickened **Folds**
- **Friability**
- Pyloric **Stenosis**

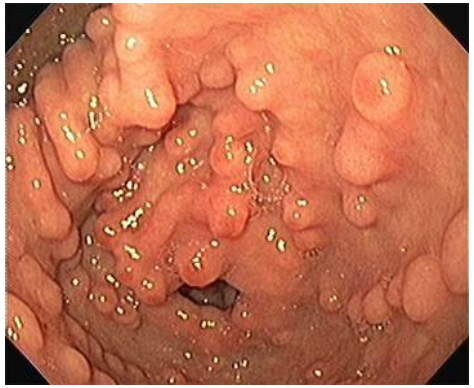
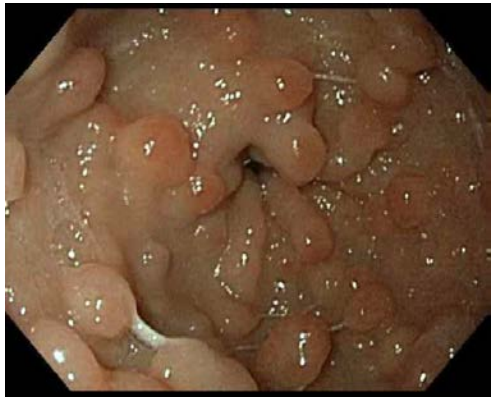
Hirano DDW 2019

Gastric Endoscopic Reference System

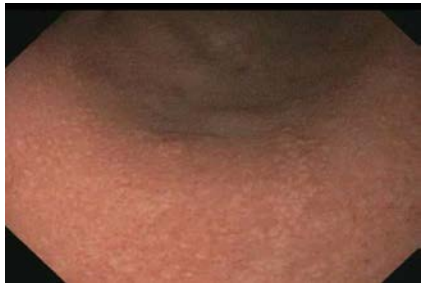
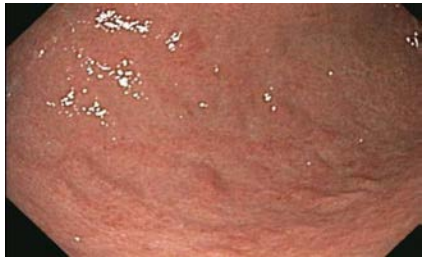
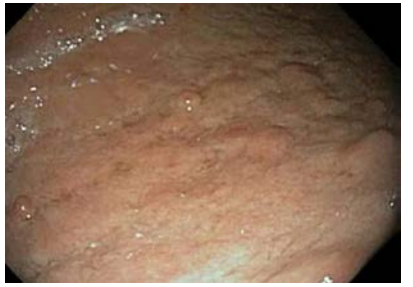
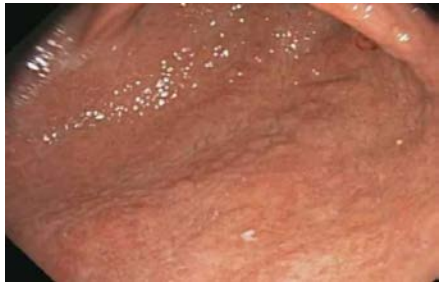
Erosions/Ulcer


Raised Lesion

Granularity

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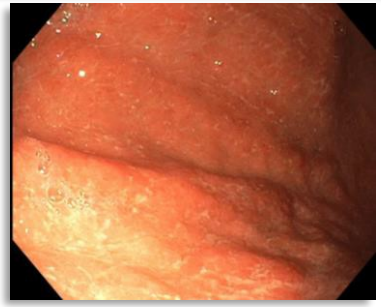
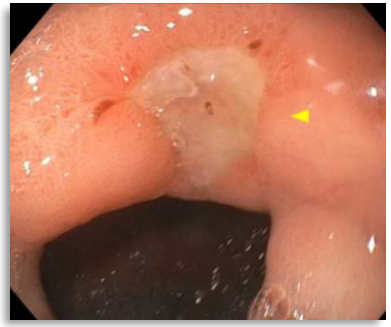
Hirano DDW 2019

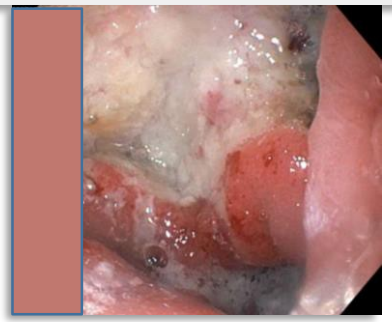
Severity of the Disease Presentation can Vary

Northwestern Medicine

Mild	Moderate	Severe	Clinical Presentation
• Mild clinical sxs and endoscopic appearance • Intermittent symptoms	• More persistent symptoms and endoscopic abnormalities • Starting to have impact on QOL	• Significant symptoms and complications from disease such as GI bleeding/perforation • Marked impact on QOL	• Determines overall workup and treatment plan





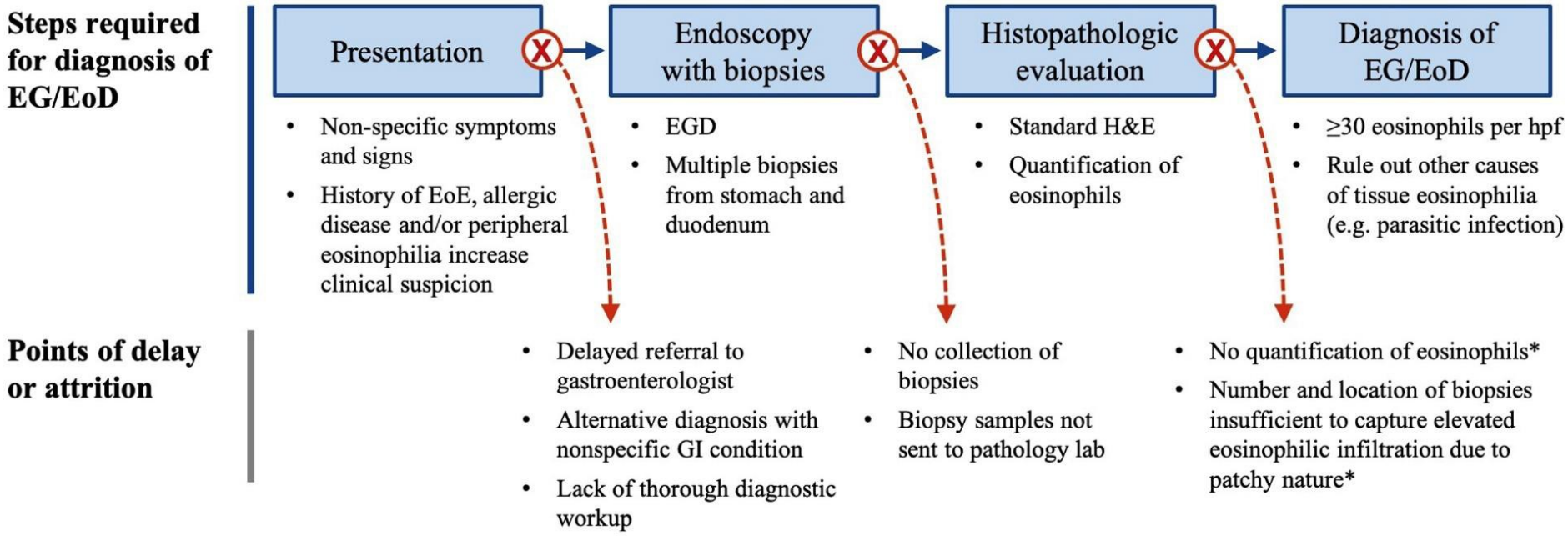


Eosinophilic Gastrointestinal Disease: *Overview*

- Clinical Presentation
- Endoscopic Features
- Impact on Quality of Life
- Natural History and Disease Course

EGID: *Diagnostic Delay Impacts Disease Burden*

- Average Diagnostic Delay
  - *5 yr prior to presentation*
- Average Duration of Symptoms
  - *8.8 yr prior to presentation*



Pesek...Dellon. Am J Gastroenterol 2019 Jun;114(6):984-994
Chehade et al. J Allergy Clin Immunol Pract May 2021.
Gonsalves N et al. Gastroenterology. 2020;158:s43.

EGID: *Diagnostic Delay Impacts Disease Burden*

- Average Diagnostic Delay
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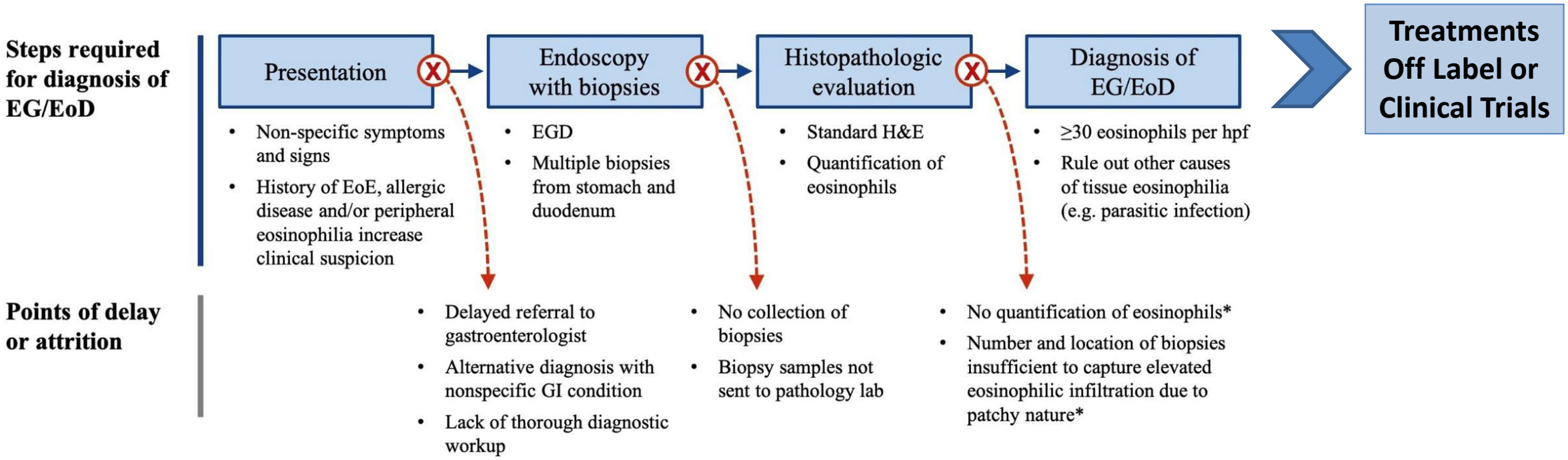


Pesek...Dellon. Am J Gastroenterol 2019 Jun;114(6):984-994
Chehade et al. J Allergy Clin Immunol Pract May 2021.
Gonsalves N et al. Gastroenterology. 2020;158:s43.

EGID:
Impact on HRQOL and Disease Burden

- Pts w/ EG/EGE completed semi-structured interviews assessing common domains of HRQOL
  - Psychosocial Impact of Diagnosis
  - Impact on Social Relationships
  - Financial Impact
  - Impact on the Body

- *Patients mood before and after diagnosis – relief at having a plan*
- *Missed work/school/social events for fear of getting symptoms/social isolation*
- *Financial cost with medications, formula, food, repeated procedures*
- *Body imaging and strain on health and activity*

Bedell et al. Dig Dis Sci 2018;63(5):1148-57..

EGID:
Impact on HRQOL and Disease Burden

- High Patient Disease Burden in EGID
  - Non-EoE Egid more frequent and non-specific sxs of nausea, abd pain, diarrhea, constipation bloating
  - Higher frequency of fatigue and isolation

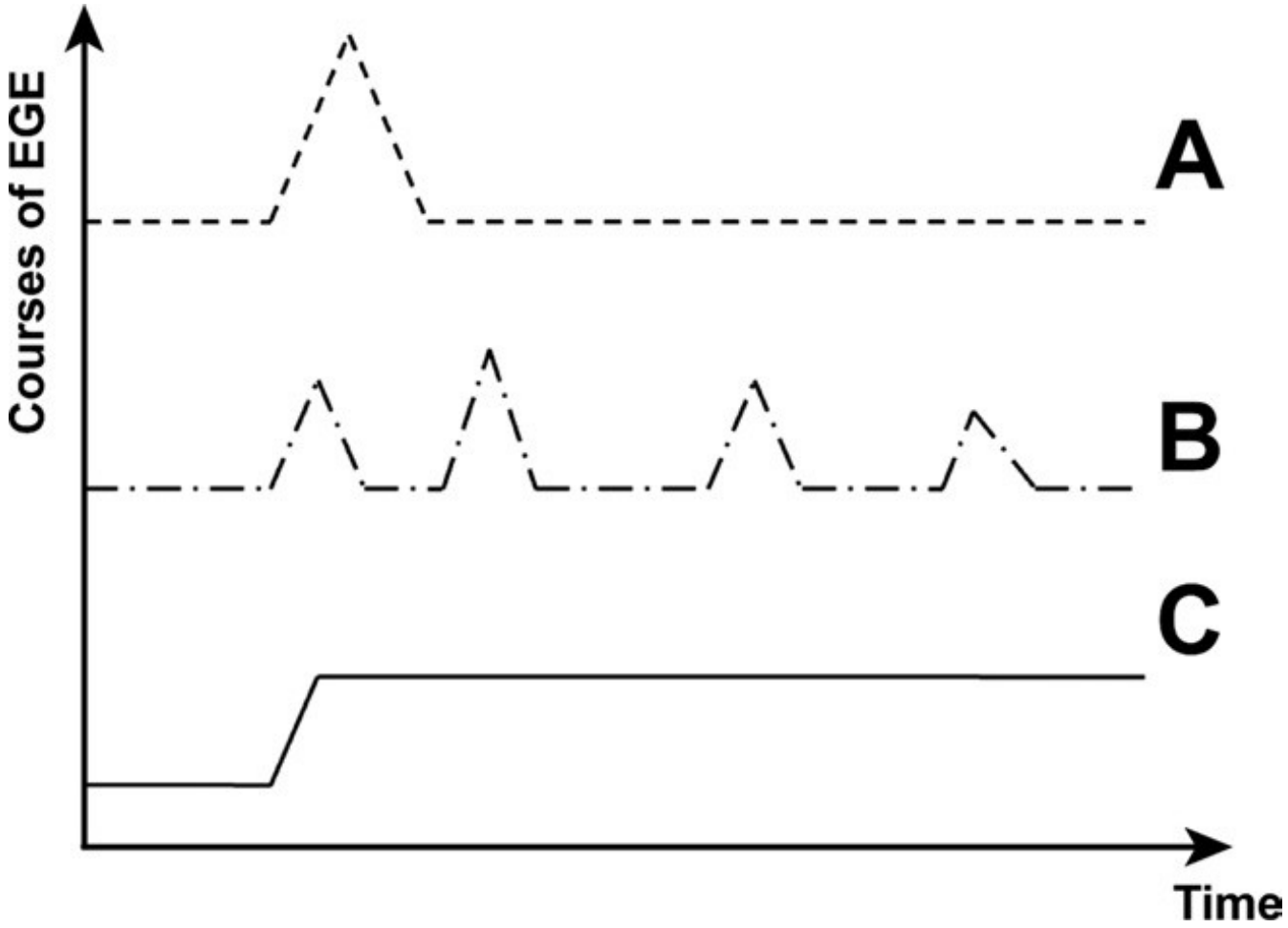
Jensen et al. JPGN Oct 2020; 71(4):524-29.

Eosinophilic Gastrointestinal Disease: *Overview*

- Clinical Presentation
- Endoscopic Features
- Impact on Quality of Life
- Natural History and Disease Course

EGE- Gastric Disease

Variations in Disease Course Suggests Chronicity of Disease



0% single flare, no relapse**

33% multiple flares and periods of full remission

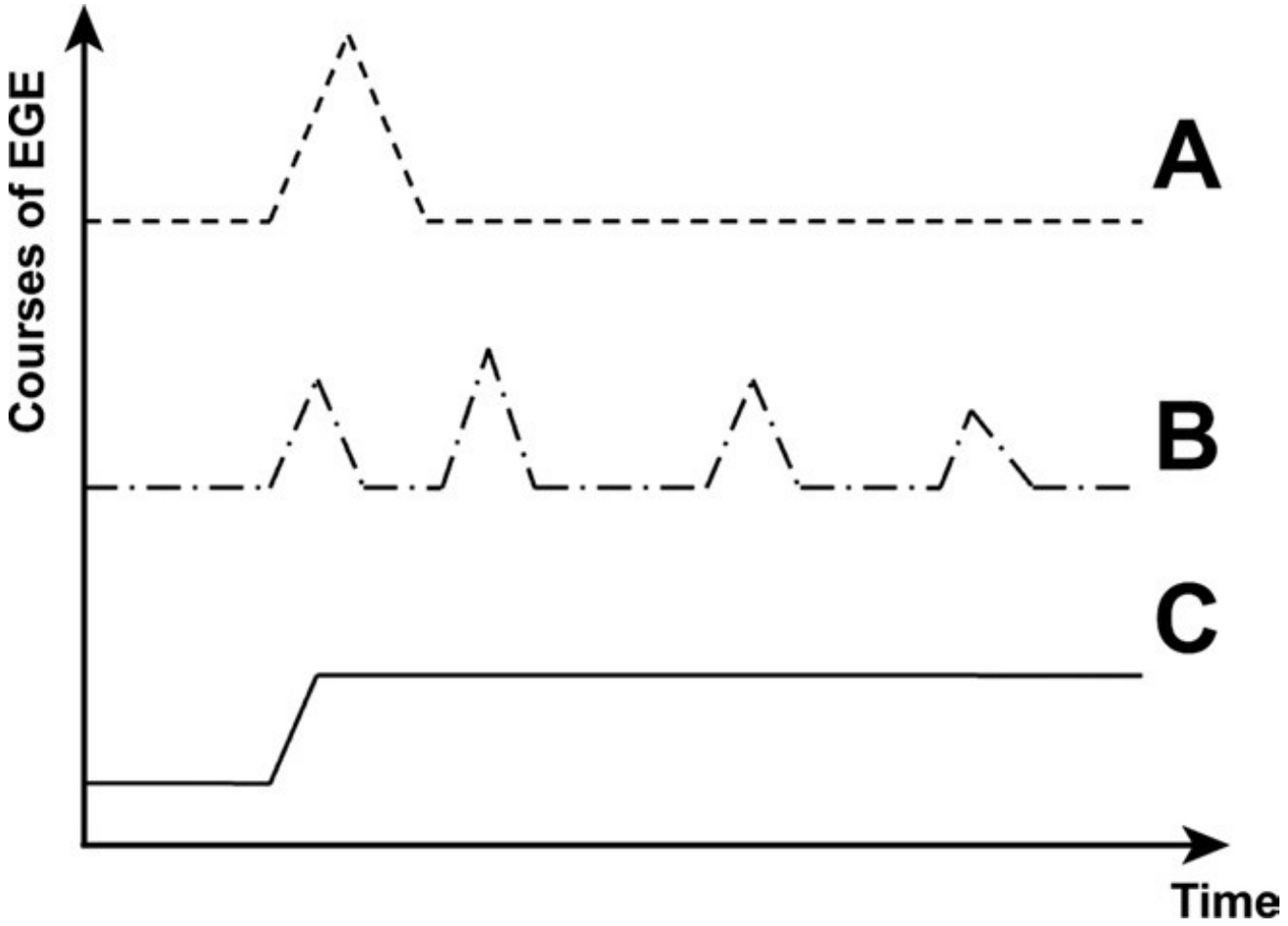
67% continuous course

*EGE defined as involvement of any segment of GI tract

- Pineton De Chambrun, et al. *Clin Gastroenterol Hepatol.* 2011;9:950-956

EGE- Proximal Small Bowel

Variations in Disease Course Suggests Chronicity of Disease



20% single flare, no relapse**

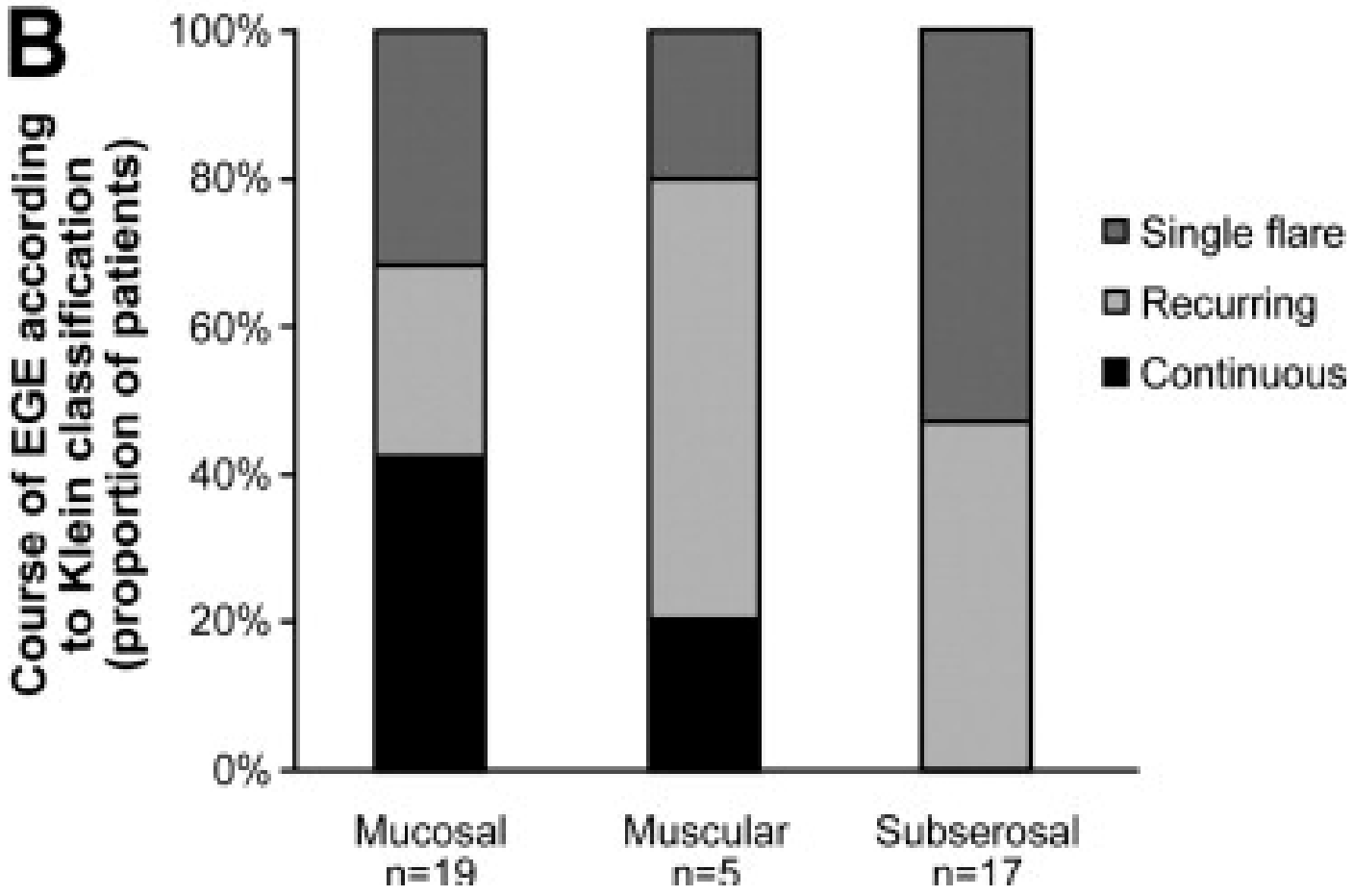
60% multiple flares and periods of full remission

20% continuous course

*EGE defined as involvement of SB and

- Pineton De Chambrun, et al. *Clin Gastroenterol Hepatol.* 2011;9:950-956

Outcomes by Subtype



- Pineton De Chambrun, et al. *Clin Gastroenterol Hepatol.* 2011;9:950-956

EGE
Variations in Disease Course Suggests Chronicity of Disease

Japanese survey study

- **Detailed data for 786 patients (39% eoe, 61% non- EoE)**
- **SB (62%), stomach (49%)**

66% of patients had continuous disease

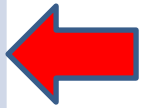
Most non-EoE EGIDS were persistent and severe

Restriction of activity, weight loss, surgery and hypoproteinemia more common in pediatric patients

- Yamamoto M, JACI In practice (2021)

EGE
Variations in Disease Course Suggests Chronicity of Disease

Natural History	Age 0-4y (%)	5-17yr (%)	>18yr (%)
Continuous Type	38	75	65
Single Flare	46	3	24
Intermittent	8	5	9
Unable to classify	8	15	3



- Yamamoto M, JACI In practice (2021)

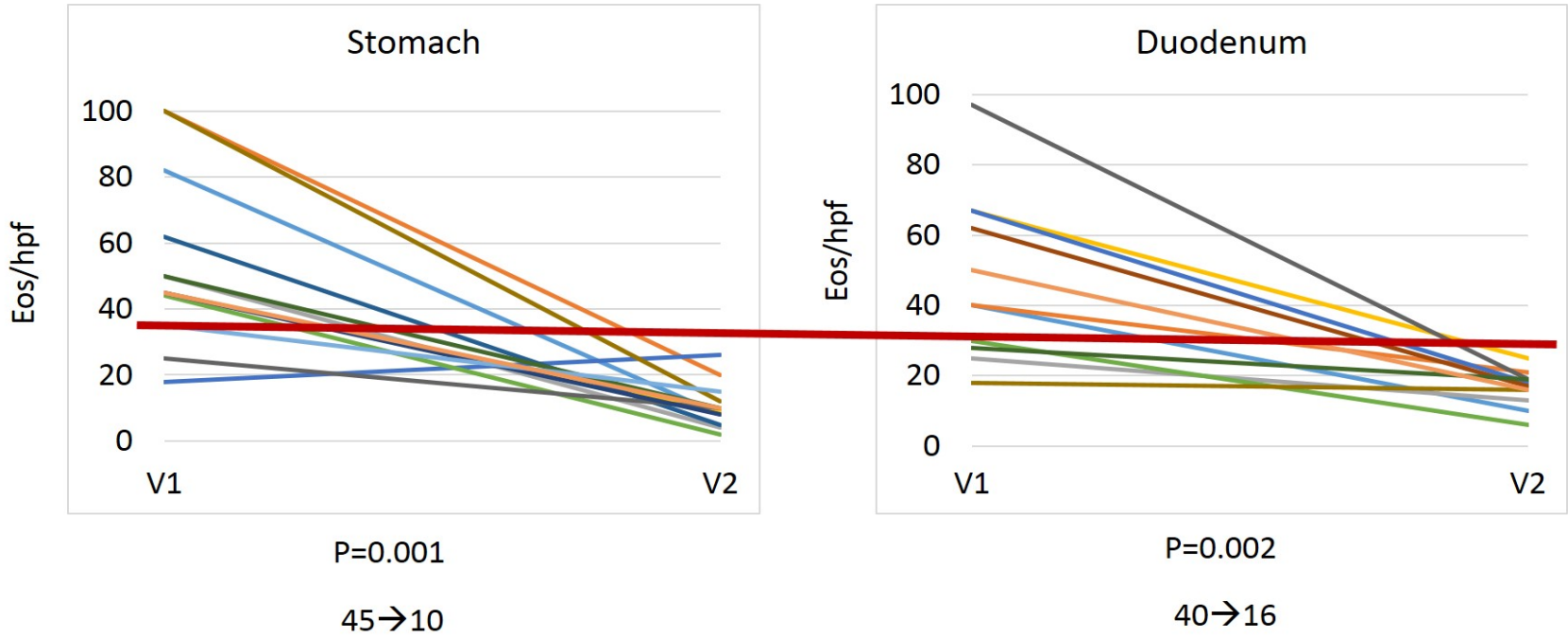
Prospective Study of Elemental Diet In Eosinophilic Gastroenteritis Nutrition Trial (ELEMENT)

15 adults (18-65 years) with histologically active EG/EGE (≥ 30 eos/hpf) in stomach and/or duodenum

- GI symptoms ≤ 1 month prior to enrollment
- Treated with elemental diet for 6 weeks

Primary endpoint:
% of participants with complete histologic remission at end of treatment

Histologic Improvement Post-Diet



- Gonsalves N, et al. *Gastroenterology*. 2020;158:S-43.

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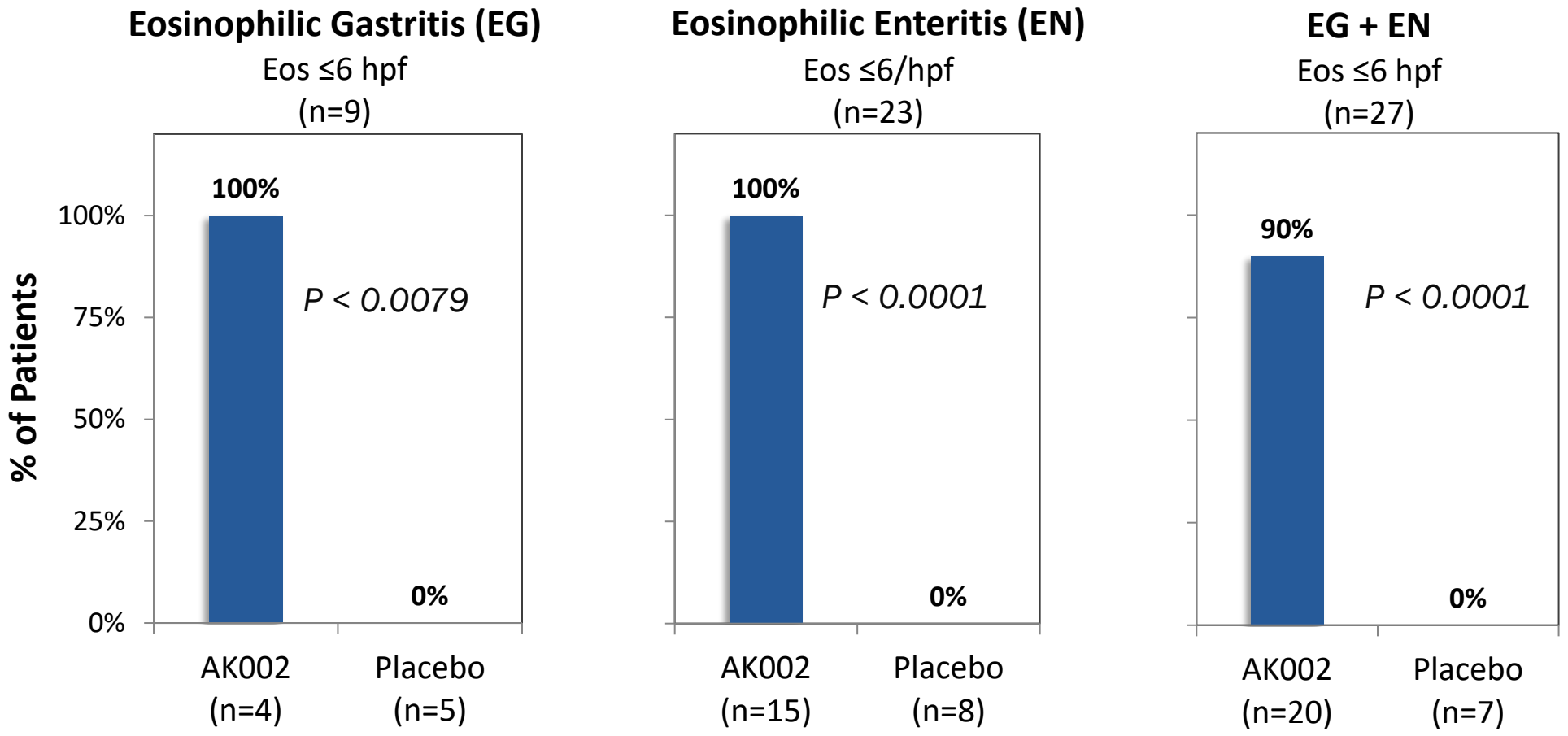
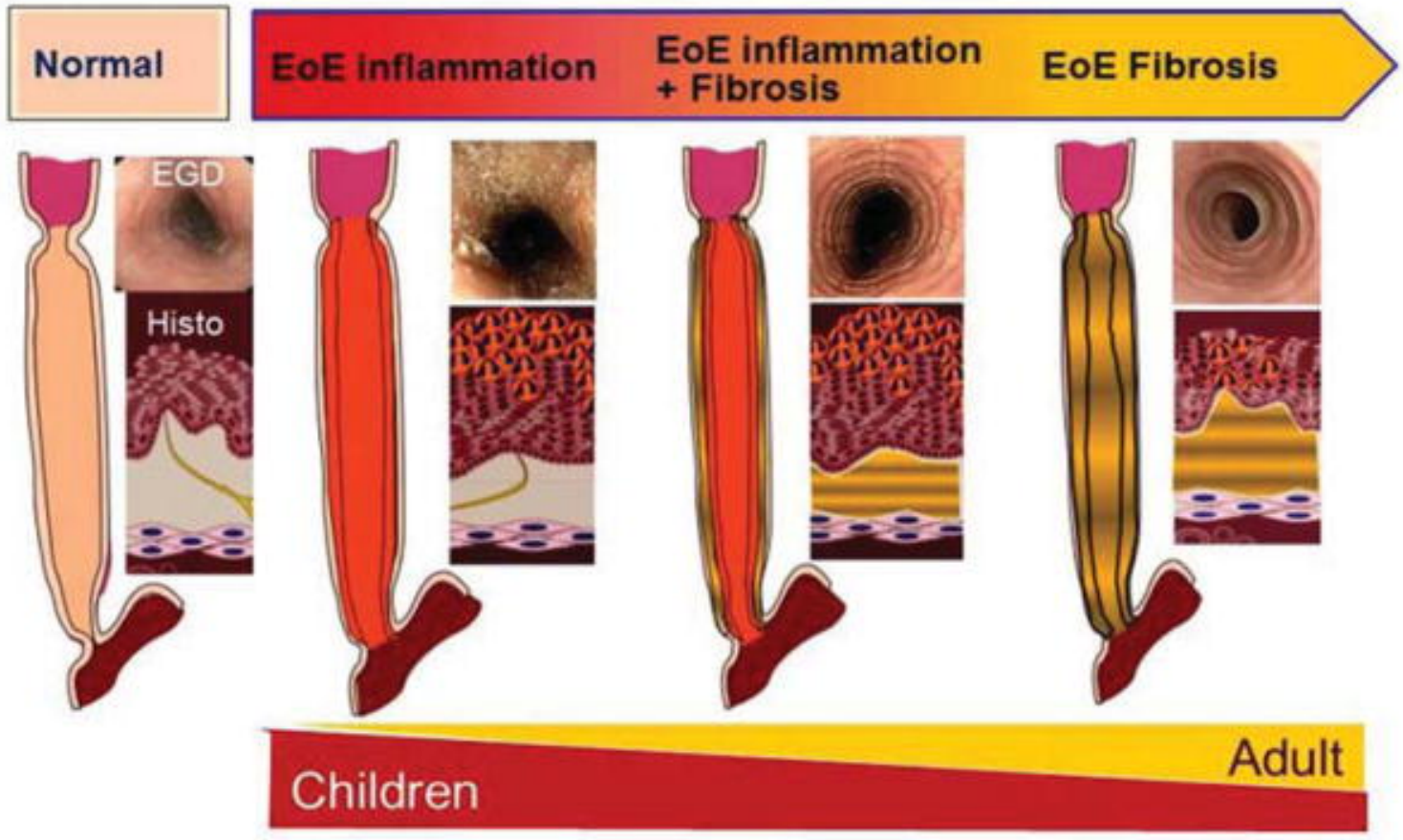
CEGiR Consortium of Eosinophilic Gastrointestinal Disease Researchers

Histologic Improvement in ENIGMA by Form of Eosinophilic GI Disease



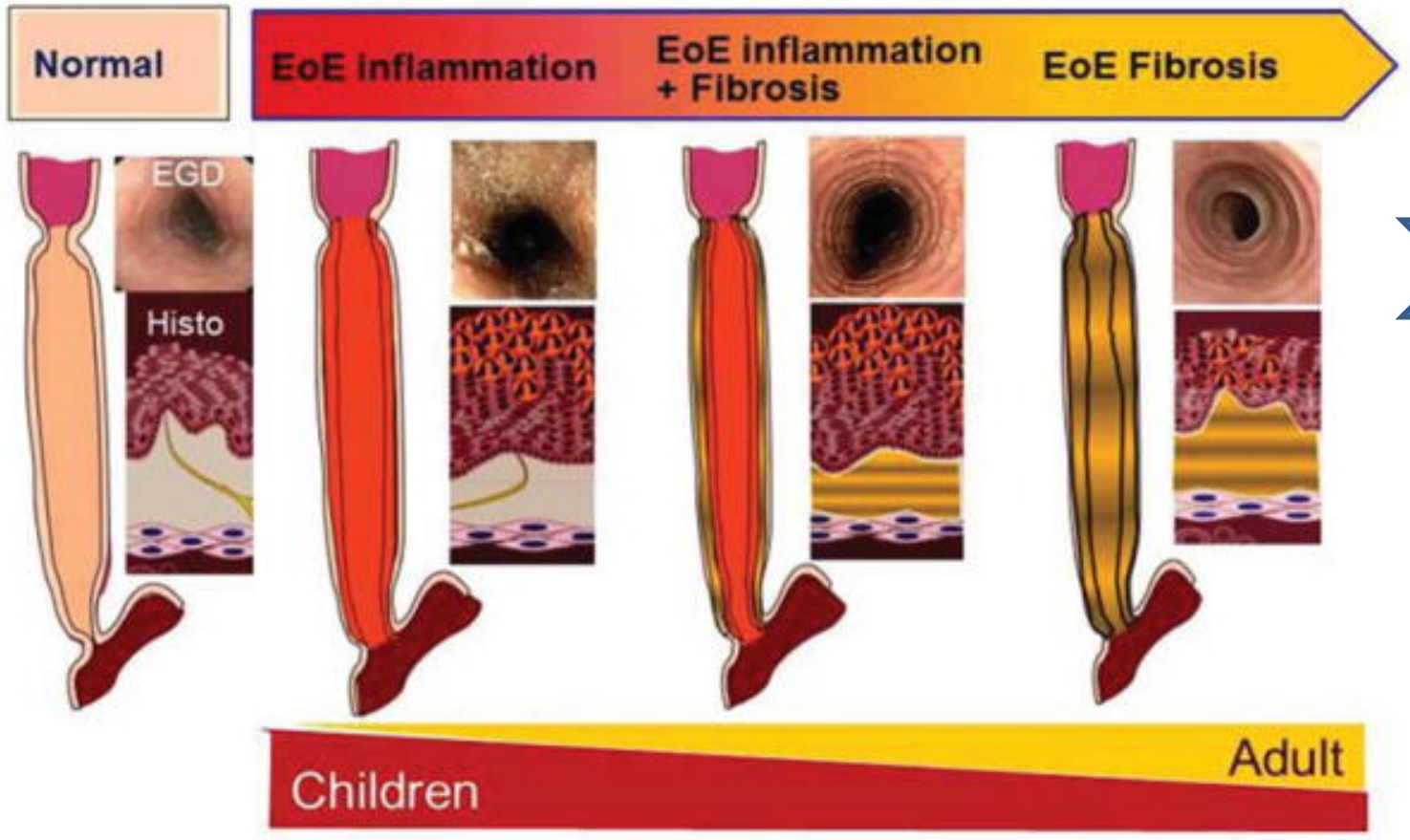
- *Dellon ES, Peterson KA, Murray JA, et al. NEJM 2020.*

Outcomes/Complications
Taking a Page from EoE



Hirano Aceves, Gastroenterol Clin North Am 2014 June;43(2):297-316.

Outcomes/Complications
Taking a Page from EoE



Hirano Aceves, Gastroenterol Clin North Am 2014 June;43(2):297-316.

Non EoE EGID

Strictures
Obstruction
Perforation
Anemia/Bleeding
Malnutrition
Chronic Symptoms
Dec QOL
Financial Burden

No progression to Malignancy

No predictors of
Disease Progression
Or complications

Treatments are Off-label &
Clinical Trials

Eosinophilic Gastrointestinal Disease: 2021

- **Clinical Presentation**
  - *Clinico-pathologic diagnosis with chronic symptoms*
  - *Related to the organ involved AND layer of bowel wall involved*
  - *Abdominal pain, diarrhea, weight loss, nausea, vomiting, bloating, early satiety, obstruction*

- **Endoscopic Features**
  - *Erythema, Nodularity, Erosions, Ulcerations, Thickened Folds, Pyloric Stenosis*

- **Signs/Labwork**
  - *Often suggestive of malabsorption – anemia, peripheral eosinophilia, low protein*

- **Outcomes/Natural History**
  - *Chronic disease and area of unmet need*
  - *Significant Impact on QOL*

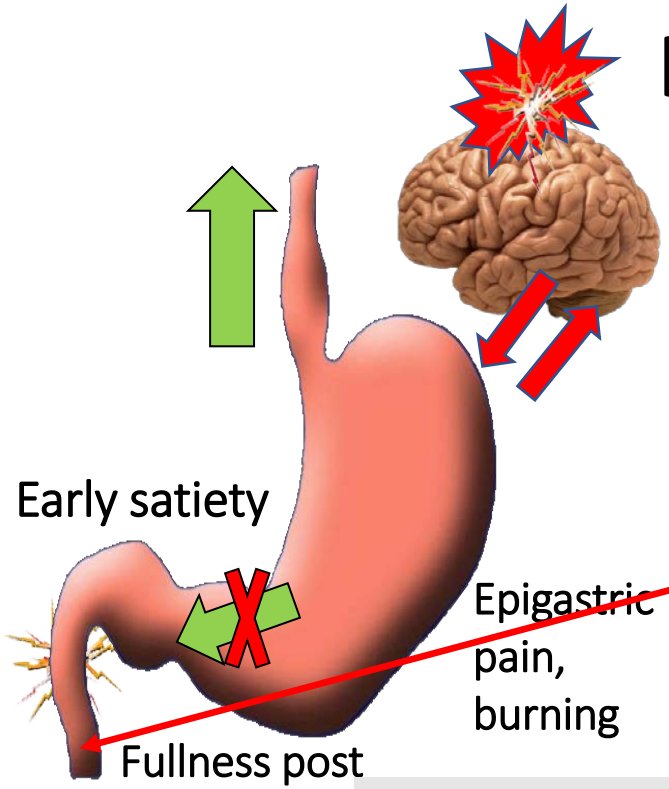
Thank you!

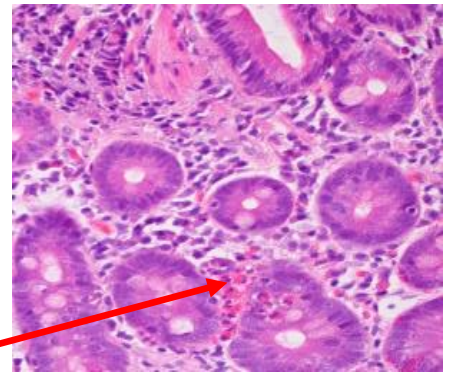
Nirmala Gonsalves, MD, AGAF
Professor of Medicine
Division of Gastroenterology & Hepatology Northwestern University- Feinberg School of Medicine
July 21, 2021

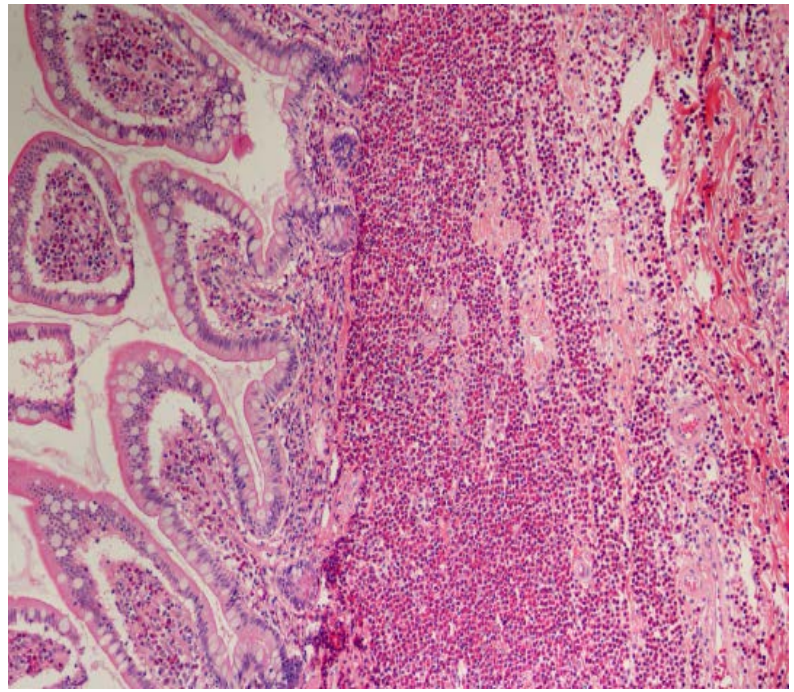
Northwestern Medicine®

Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI):
Eosinophilic Gastrointestinal Disorders Beyond EoE

Alternative etiologies for gastrointestinal mucosal eosinophilia







Nicholas J. Talley AC, MD, PhD

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Talley & Ford. *N Engl J Med* 2015:373:1853-63

Ford AC, Mahadeva S, Carbone MF, Lacy BE, Talley NJ. *Lancet*. 2020;S0140-6736(20)30469-4.

Disclosures

Grant / Research Support

HVN National Science Challenge NZ (no financial support)

Patents

Biomarkers of irritable bowel syndrome (#12735358.9 -1405/2710383 and (#12735358.9 -1405/2710384)

Licensing Questionnaires (Mayo Clinic) Talley Bowel Disease Questionnaire, Mayo Dysphagia Questionnaire

Nestec European Patent Application No. 12735358.9

Singapore 'Provisional' Patent NTU Ref: TD/129/17 "Microbiota Modulation Of BDNF Tissue Repair Pathway"

Editorial

Medical Journal of Australia (Editor in Chief) (2015-current)

Up to Date (Section Editor) (current)

Precision and Future Medicine, Sungkyunkwan University School of Medicine, South Korea (2017-present)

Boards

GESA Board Member. Gastroenterology Society of Australia (2017- 2019)

Committees

Australian Medical Council (AMC) Council Member (2016-2019)
MBS Review Taskforce (current)
NHMRC Principal Committee, Research Committee (2016-2021)
Asia Pacific Association of Medical Journal Editors (APAME) (2018-)
AAHMS member

Consultancies

Allakos USA 2019
Viscera Labs, USA 2019
Progenity Inc. San Diego, USA
Sanofi-aventis, Sydney
Censa, Wellesley, MA, USA
Anatara Life Sciences, Brisbane
Takeda, Japan (gastroparesis)
Aviro Health (Digestive health) 2019
ARENA Pharmaceuticals 2019

Miscellaneous

Avant Foundation (judging of research grants) (2017-2019)

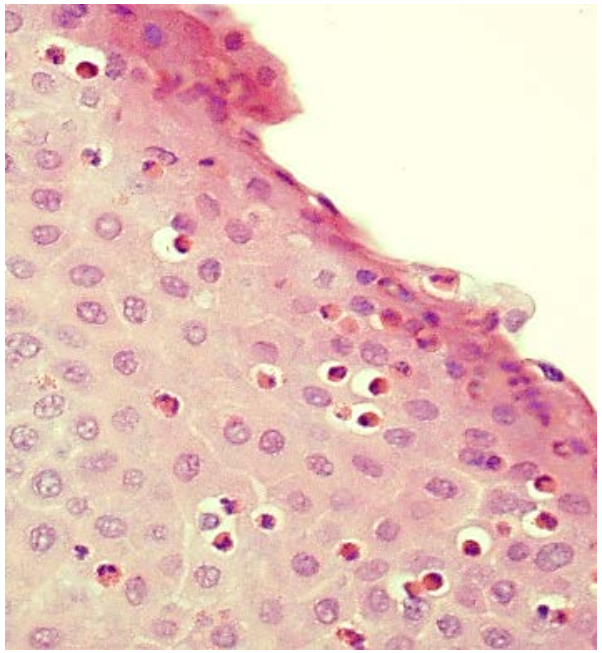
Community and patient advocacy groups

Advisory Board, IFFGD (International Foundation for Functional GI Disorders)

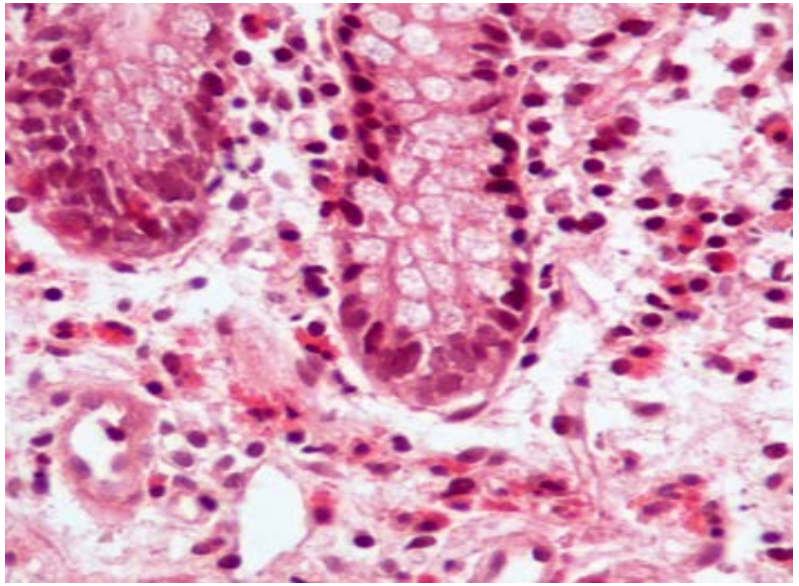
Traditional Eosinophilc GI Diseases (EGIDs)

- Rare! Linked to atopy
- EoE increasing, EGE may be increasing, EC very rare
- **EGE**: mucosal disease stomach and/or small intestine, predominant phenotype, muscularis and serosal forms rare
- **EGE**: GI symptom manifestations very similar to FGIDs, diagnostic delay common, can be debilitating

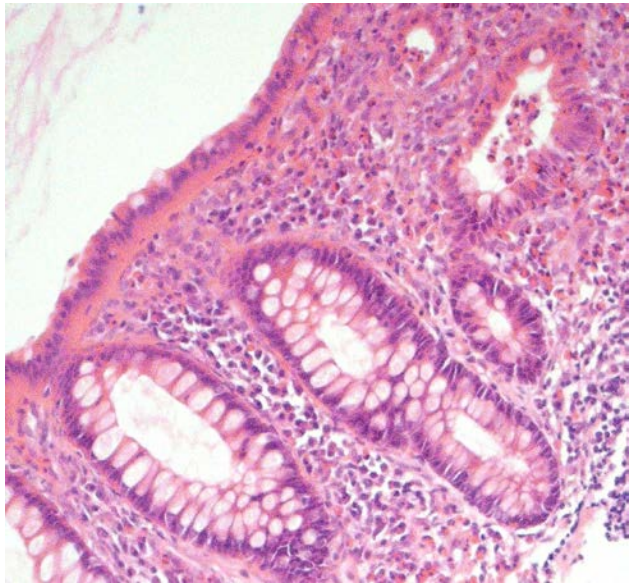
Walker MM, Potter M, Talley NJ. *Lancet Gastroenterol Hepatol.* 2018;3(4):271-280



Eosinophilic esophagitis (EoE)



Eosinophilic Gastroenteritis (EGE): includes eosinophilic duodenitis &/or gastritis (EoD/EG)

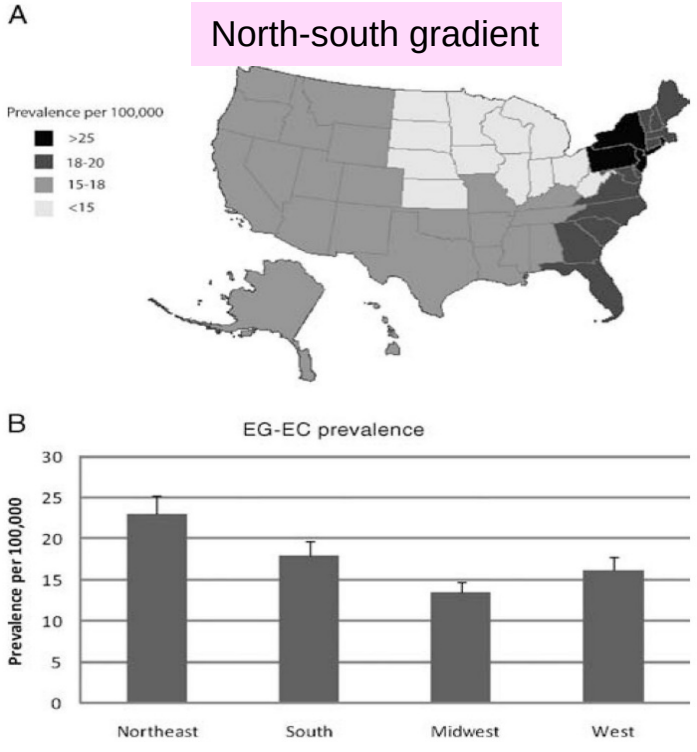


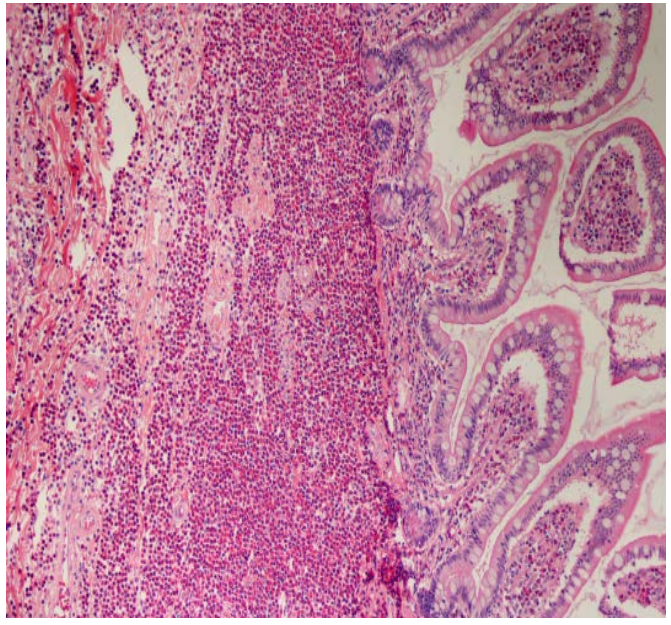
Eosinophilic Colitis (EC)

Non-EoE EGIDs reported to be RARE in the United States (< 50,000)?

- Standardized estimated prevalences (may be increasing)
- **Eosinophilic gastritis** 6.3/100,000
- **Eosinophilic gastroenteritis** 8.4/100,000
- **Eosinophilic colitis** 3.3/100,000
- Prevalence of EGE was the highest among children age <5 years

Spergel JM, Talley NJ, et al. J Pediatr Gastroenterol Nutr. 2011;52(3):300-6



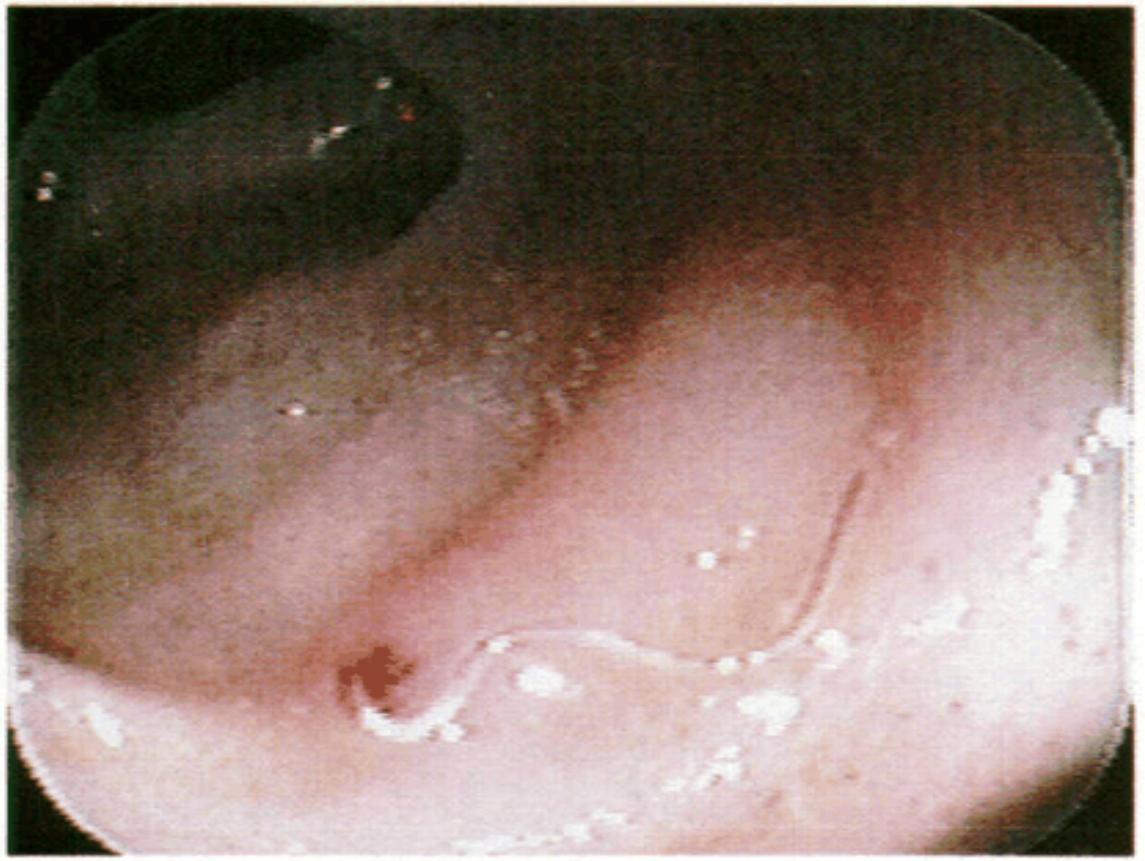


- **Mayo Clinic retrospective series**: Most with EGIDs are adults (3rd-5th decades) – mean age n=71 cases, 45 years
- Abdominal pain common (2/3)
- Nausea, vomiting, diarrhea
- Waxing and waning symptoms
- Peripheral blood eosinophilia common but *not* universal; often a normal endoscopy
- Often misdiagnosed as an FGID initially (functional dyspepsia - FD)

Chang, Talley et al. Clin Gastro Hep 2010; 8: 669-75

Differential EGID- Parasites

- *Toxocara canis*
- *Toxocara cati*
- Ascariasis
- Trichinosis
- Hookworm (Ancylostoma caninum)
- Strongyloidiasis
- Schistosomiasis



Hookworm (Ancylostoma caninum) mimics EG in the small bowel and colon clinically and pathologically; reported in Australia but worm has a worldwide distribution

- Examine the stool for ova and parasites (serology/skin testing)
  - Charcot-Leyden crystals the product of eosinophil granules
- In correct clinical setting (ileocolonic disease, dog owner), empiric mebendazole

Croese et al. 1994 | Volume 120 | Pages 369-374 Annals of Internal Medicine

Spirochetes in IBS-diarrhea, associated with colonic eosinophilia

Human Pathology (2015) 46, 277–283

ELSEVIER

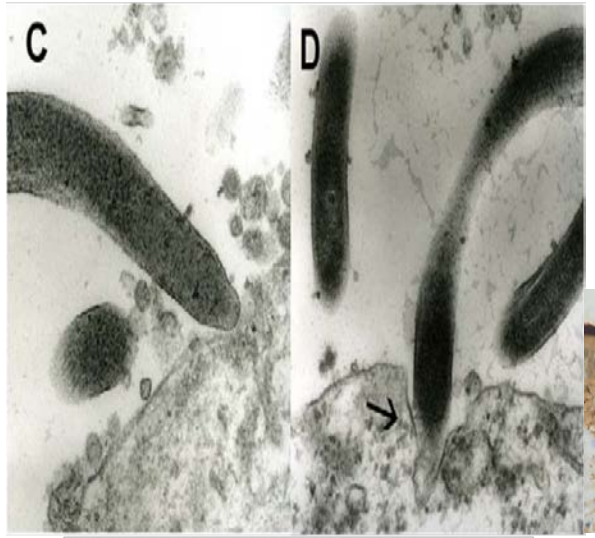
Human PATHOLOGY

www.elsevier.com/locate/humpath

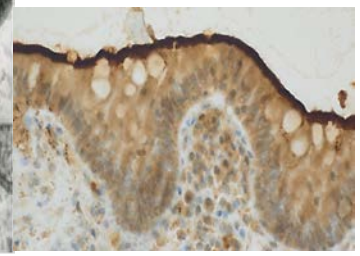
Original contribution

Colonic spirochetosis is associated with colonic eosinophilia and irritable bowel syndrome in a general population in Sweden☆,☆☆

Marjorie M. Walker BMBS, FRCPath[a,*], Nicholas J. Talley MD, PhD[b], Linn Inganäs MSc[c,d], Lars Engstrand MD, PhD[d], Michael P. Jones PhD[e], Henry Nyhlin MD, PhD[f], Lars Agréus MD, PhD[c], Lars Kjellstrom MD[g], Åke Öst MD, PhD[h], Anna Andreasson PhD[c,i]



Hampson (2011) Microbiology



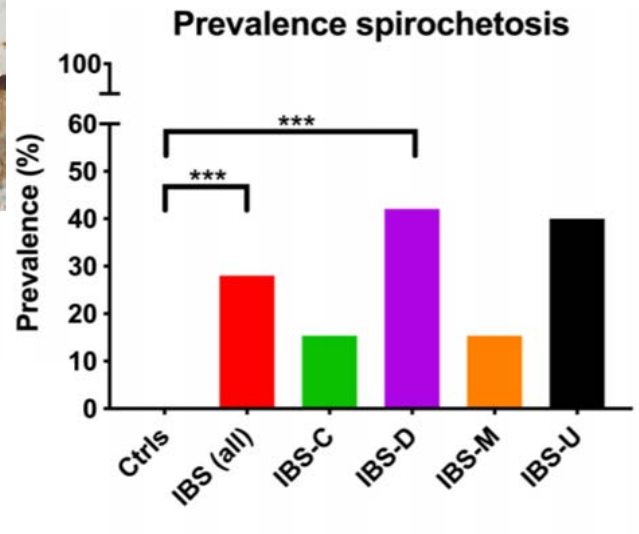
Colon

OPEN ACCESS

ORIGINAL RESEARCH

Association between *Brachyspira* and irritable bowel syndrome with diarrhoea

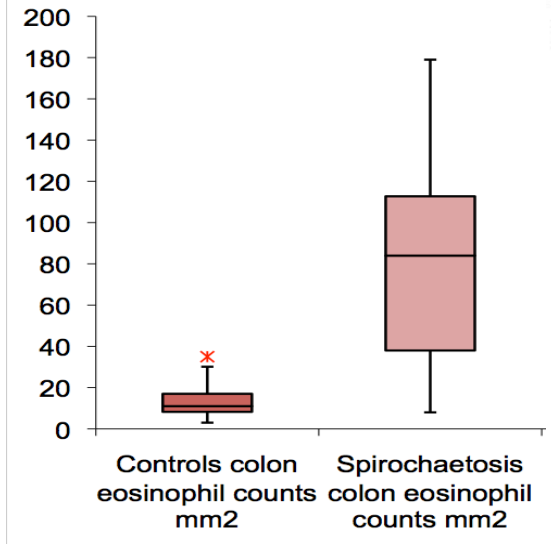
Karolina S Jabbar,[1,2] Brendan Dolan,[1] Lisbeth Eklund,[1,2] Catharina Wising,[1] Anna Ermund,[1] Åsa Johansson,[1] Hans Törnblom,[2,3] Magnus Simren,[2,3] Gunnar C Hansson [1]

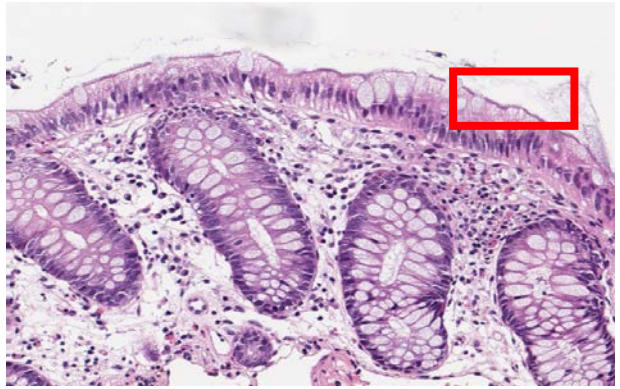


Thorell, Talley, Engstrand et al. *J Bacteriol*. 2019;201(21)

Table 2 Spirochetosis and associated conditions in a general population in Stockholm, Sweden

	Spirochetosis	No spirochetosis	OR (95% CI)	*P*
No. of subjects (%)	17/745 (2.3%)	728/745 (97.7%)		
Age (y), mean (range)	49 (27-69)	51 (19-70)		.98
% by sex (male)	53	49		.74
Rome III IBS, n (%)	6/17 (35%)	104/728 (14.3%)	3.59 (1.27-10.11)	.015
Polyps	5/17 cases (29%)	206/728 (28.3%)	(25.1-31.8)	.53
Diverticular disease	2/17 (12%)	128/728 (17.7%)	(14.9-20.6)	.53





Drug induced GI eosinophilia

Proton pump inhibitors and duodenal eosinophilia (mm^2):

FD patients, no history of PPI:	331.07 ± 16.93
Same patients after commencing PPI:	182.63 ± 22.62*
Healthy Volunteers with no PPI history:	114.6 ± 8.83
Same Healthy Volunteers after commencing PPI:	229.22 ± 21.01*

*P <0.0001

Wauters et al. Gastroenterology 2021;160:1521–1531

- Minority confirmed by re-challenge

Systematic review drug induce GI eosinophilia

Case report:

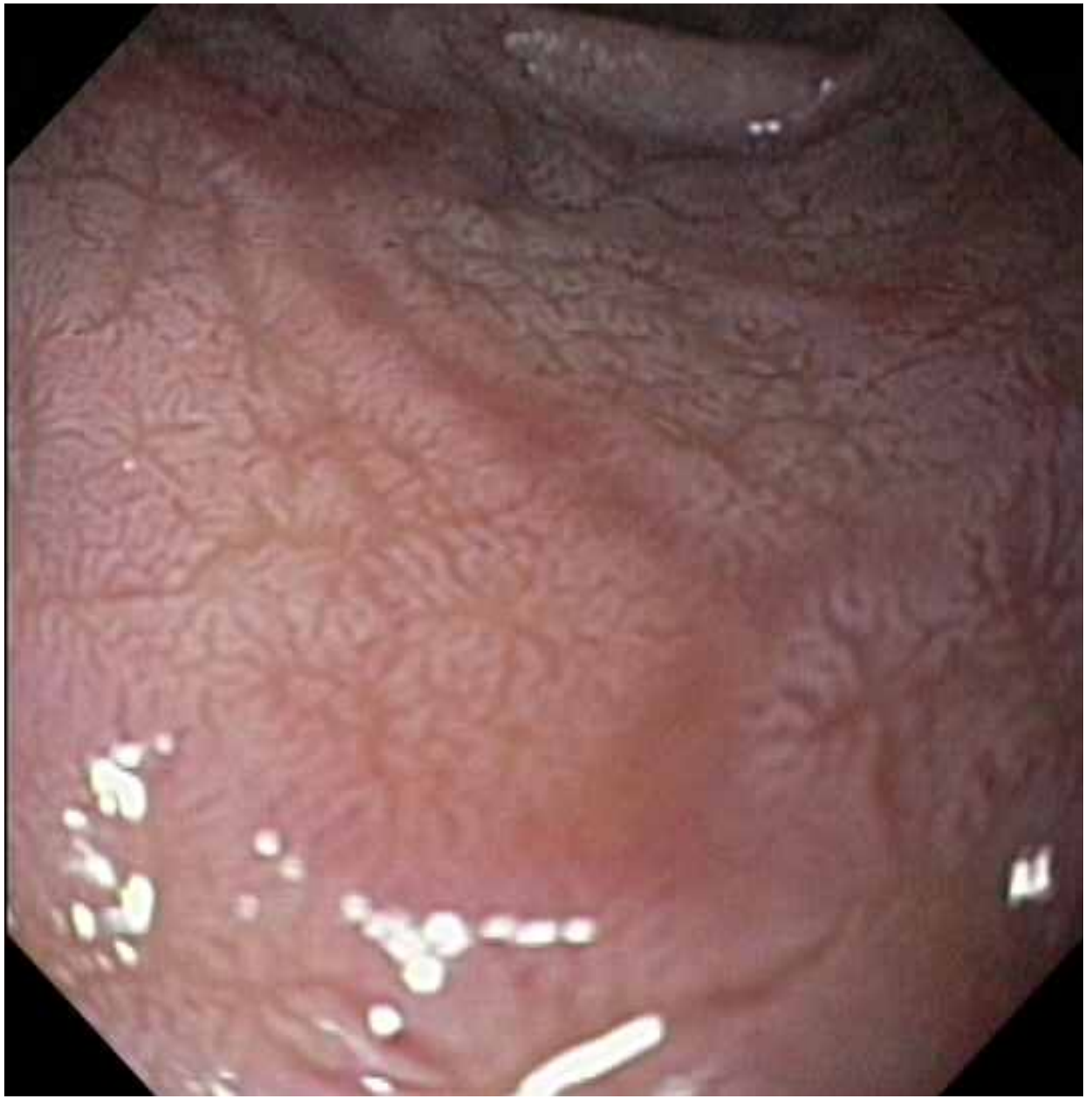
- Enalapril
- Pentostatin
- Gemfibrozil
- Carbamazepine
- TNF-antagonist in ulcerative colitis
- Infliximab and Adalimumab in Crohn's
- Immune checkpoint inhibition, nivolumab
- Celcoxib in the context of Churg-Strauss
- Alpha-Interferon for hepatitis C

Case-series:

- Post- liver transplant immunosuppression

Celiac disease

- Activated eosinophils in celiac mucosa[1,2]
- Release cytotoxic proteins - MBP
- Contribute to mucosal damage
- Duodenal eosinophil counts are higher in celiac disease than controls, but not associated with presenting symptoms or markers of disease severity[3]

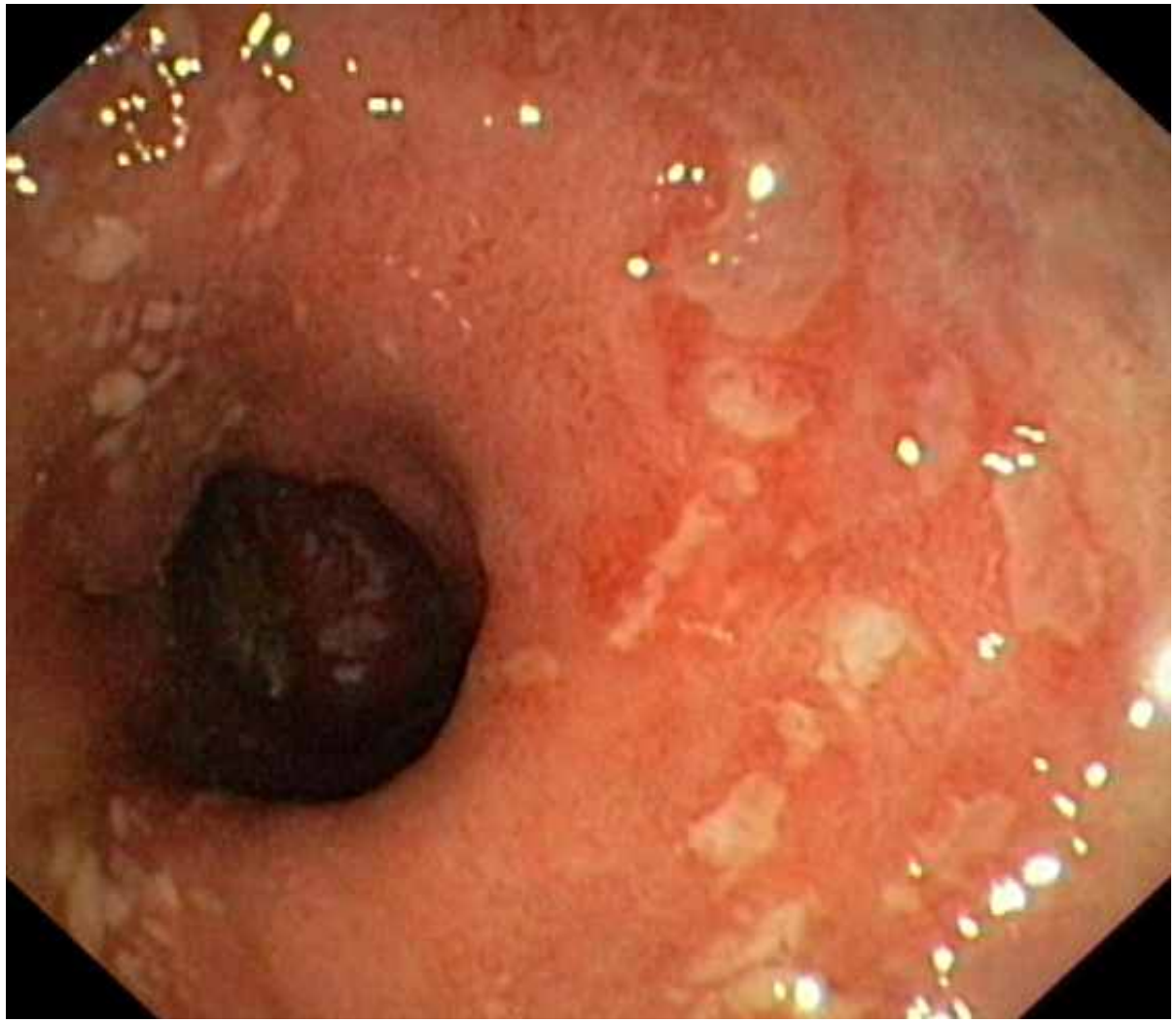


[1]Talley et al. Gastroenterology. 1992;103:137-45.
[2]Colombel et al. Gut. 1992;33:1190-4
[3]Potter MD, Hunt JS, Walker MM, Jones M, Liu C, Weltman M, Talley NJ. Scand J Gastroenterol. 2020;55:780-784

Inflammatory Bowel Disease

- Correlation with severity of disease and eosinophil number
- ↑Eosinophils and IL-5+ cells may indicate enhanced cellular activation with degranulation
- ↑IL-5+ cells reflect predominant local Th2 response in UC compared with Crohns disease

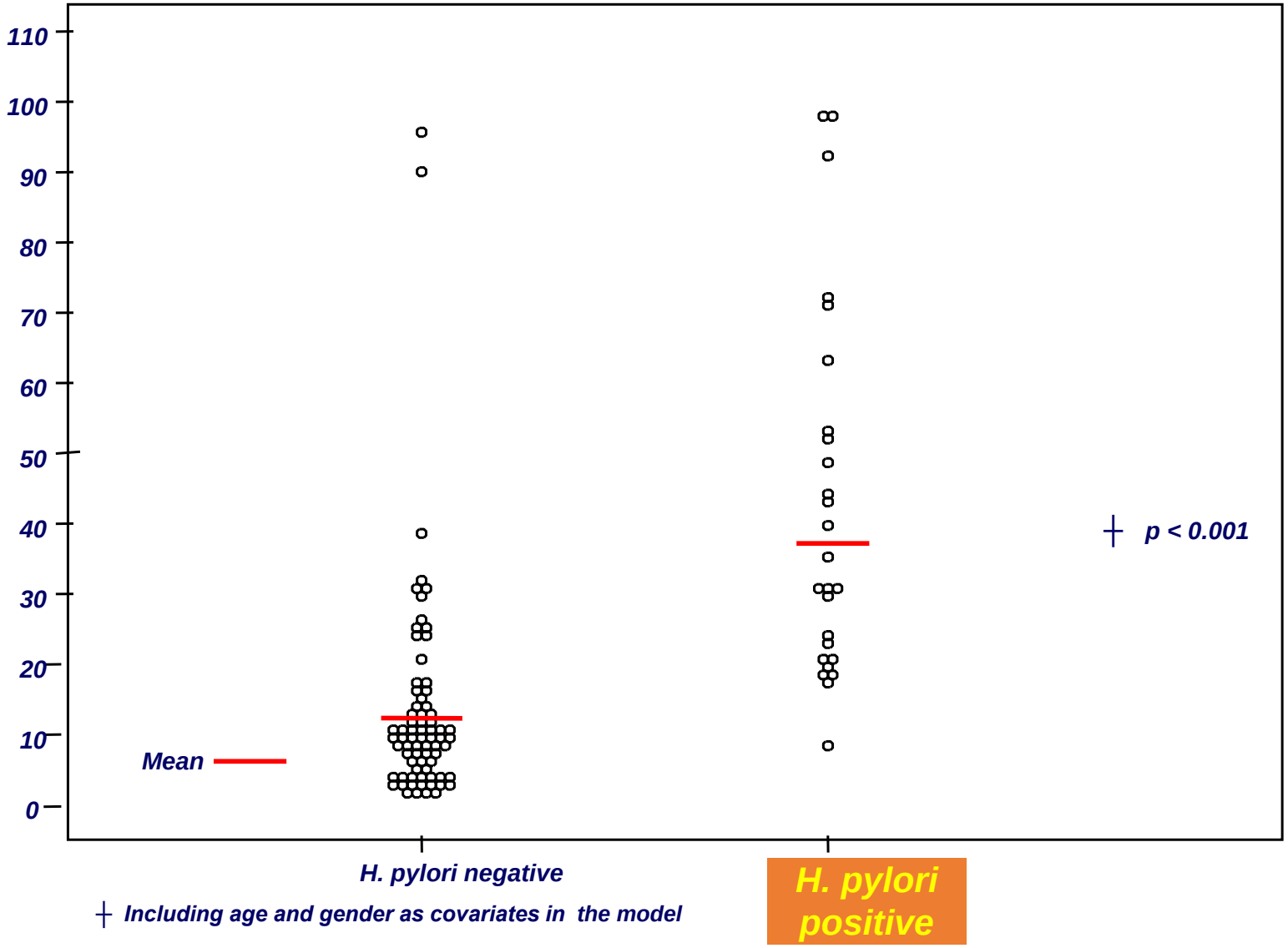
➢ Role?



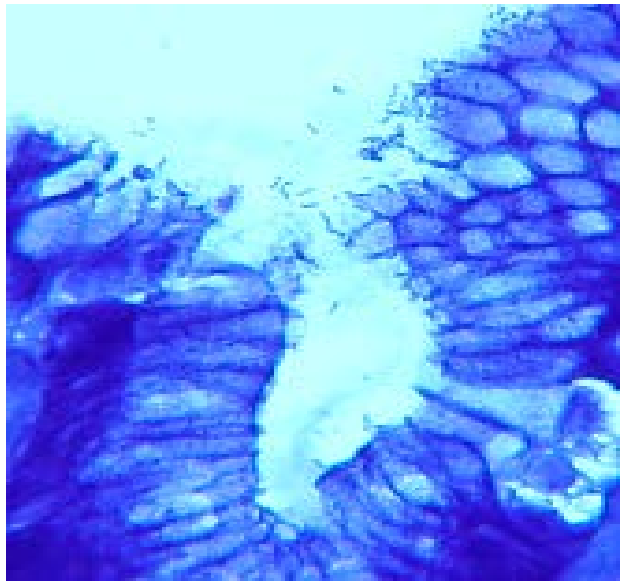
Carvalho AT J Clin Gastroenterol 2003;36:120-5

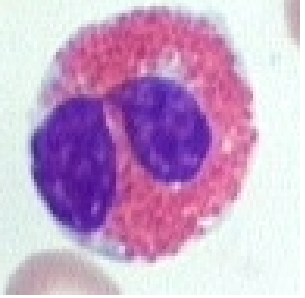
Gastric Eosinophilia and *H. pylori*

Max. gastric eos counts
Hp+ve/ Hp-ve subjects



Talley et al. Clin Gastroenterol Hepatol. 2007 5:1175-83





Hypereosinophilic syndrome (HES) with gastrointestinal involvement

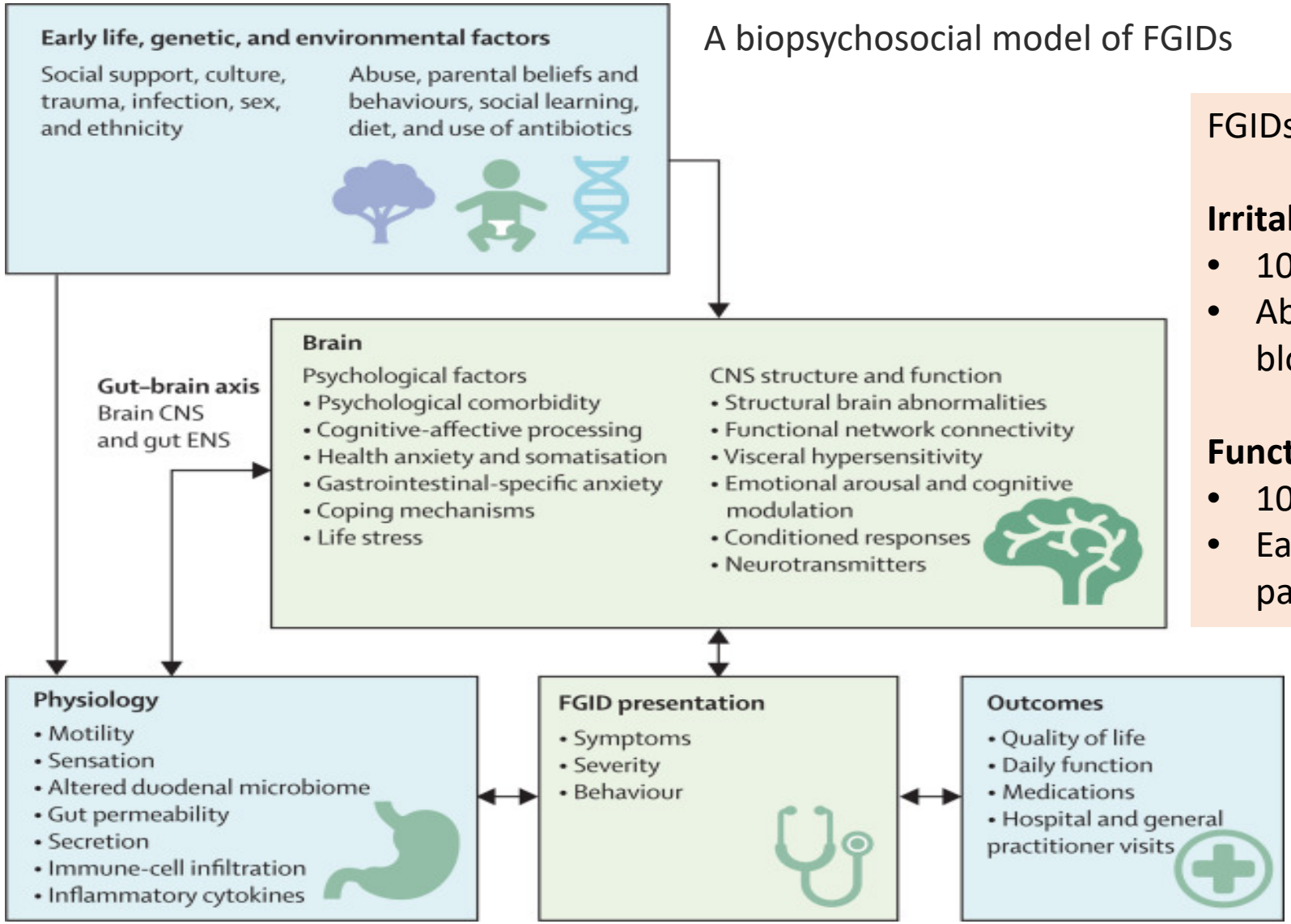
Diagnostic criteria for HES:

- Persistent eosinophilia - > 1500 cells/mm^2 for 6 months
- Lack of known causes for eosinophilia (e.g. parasitic or allergic triggers)
- Symptoms and signs of organ system involvement
- Patients with EGIDs and **blood eosinophil counts**

  > 1500/mm^2 meet the diagnostic criteria
- Patients with EGIDs do *not* have the high risk of life threatening complications associated with classic idiopathic HES

Functional gastrointestinal disorders (FGIDs, or disorders of gut-brain interactions - DGBIs)

A biopsychosocial model of FGIDs



FGIDs defined ONLY by symptoms include -

Irritable bowel syndrome (IBS):

- 10% world-wide
- Abdominal pain linked to bowel disturbance, bloating common

Functional dyspepsia (FD):

- 10% world-wide
- Early satiety, postprandial fullness, epigastric pain/burning

Unexplained!

Black CJ, Drossman DA, Talley NJ, Ruddy J, Ford AC. *Lancet*. 2020;S0140-6736(20)32115-2.

EGIDs and FGIDs (DGBIs)

Eosinophils implicated in chronic unexplained GI symptoms

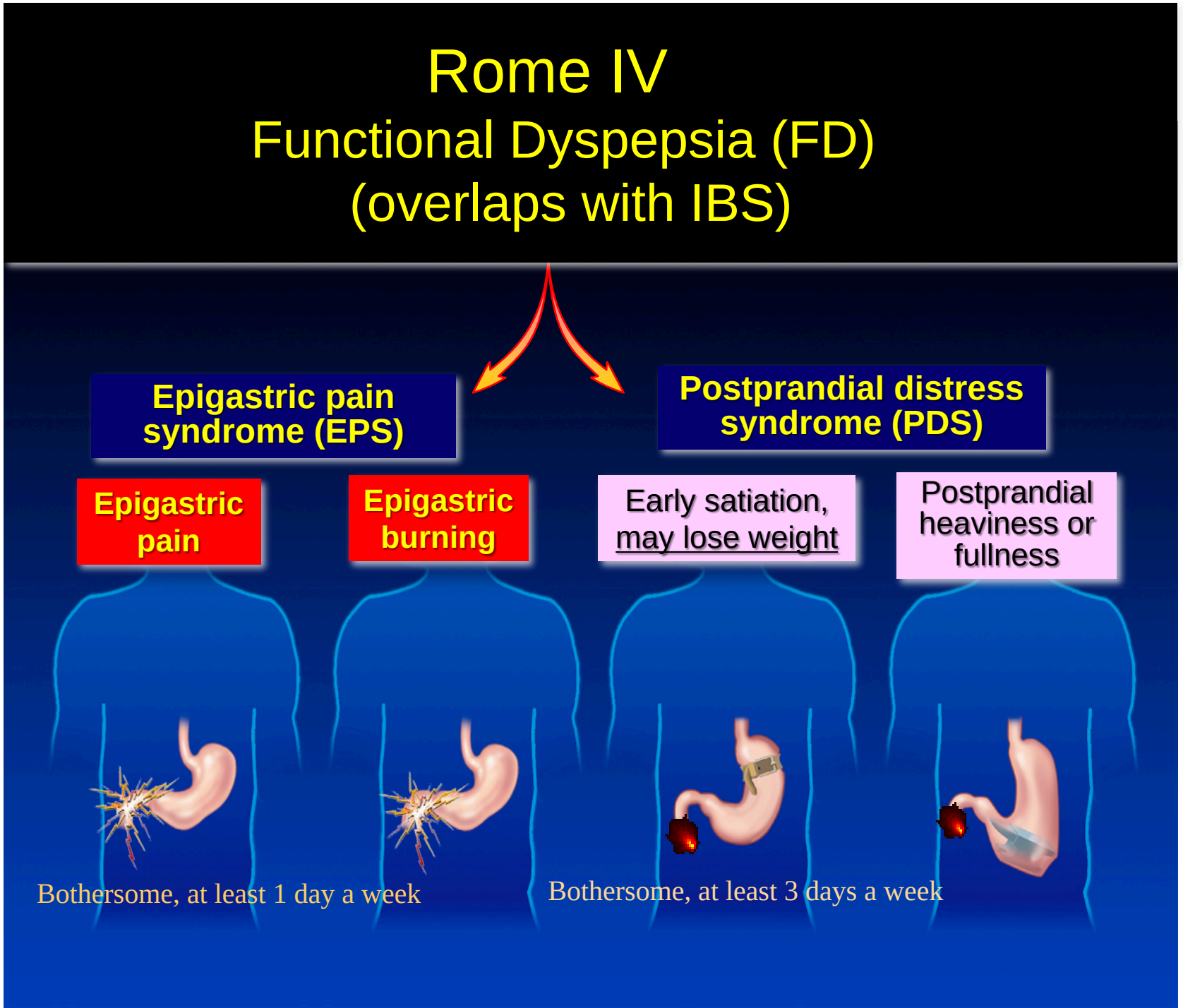
1990	Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. Gut. 1990 Jan;31(1):54-8.
1992	Talley NJ, Kephart GM, McGovern TW, Carpenter HA, Gleich GJ. Deposition of eosinophil granule major basic protein in eosinophilic gastroenteritis and celiac disease. Gastroenterology. 1992 Jul;103(1):137-45.
1997	Kalantar SJ, Marks R, Lambert JR, Badov D, Talley NJ. Dyspepsia due to eosinophilic gastroenteritis. Dig Dis Sci. 1997 Nov;42(11):2327-32.
2007	Talley NJ, Walker MM, Aro P, Ronkainen J, Storskrubb T, Hindley LA, Harmsen WS, Zinsmeister AR, Agréus L. Non-ulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. Clin Gastroenterol Hepatol. 2007 Oct;5(10):1175-83.
2021	#DDW2021 Talley et al. Endoscopy and systematic biopsy of patients with chronic gastrointestinal symptoms leads to high discovery rate of patients who meet histologic criteria for eosinophilic gastritis and/or eosinophilic duodenitis. Gastroenterology.

IBS and FD: may share a common pathogenesis

- FD overlaps with IBS more than expected by chance!
- N=807 Rome IV IBS (UK)
- Overlap with FD: 446 (55.3%)
- 451 (55.9%) successfully followed up 1 year
- IBS/FD overlap more severe symptoms, more doctor consults, more treatments, more psychological distress, greater impairment QoL
- Similar findings from Australia

Barberio B et al. Clin Gastroenterol Hepatol. 2021: S1542-3565(21)00445-6

von Wulffen M et al. Dig Dis Sci. 2019;64(2):480-486



Functional dyspepsia (PDS, not EPS) increasing

- Östhammar community, Sweden
- All inhabitants above 18 years born day 3, 12, 24 every month
- 4 repeated validated ASQ postal surveys
  - 1988, 1989, 1995 and 2011 → 23 year follow up
- Total 1884 participants participated on 4509 occasions
  - On average 2.4 occasions each

- 444 participated in all 4 surveys

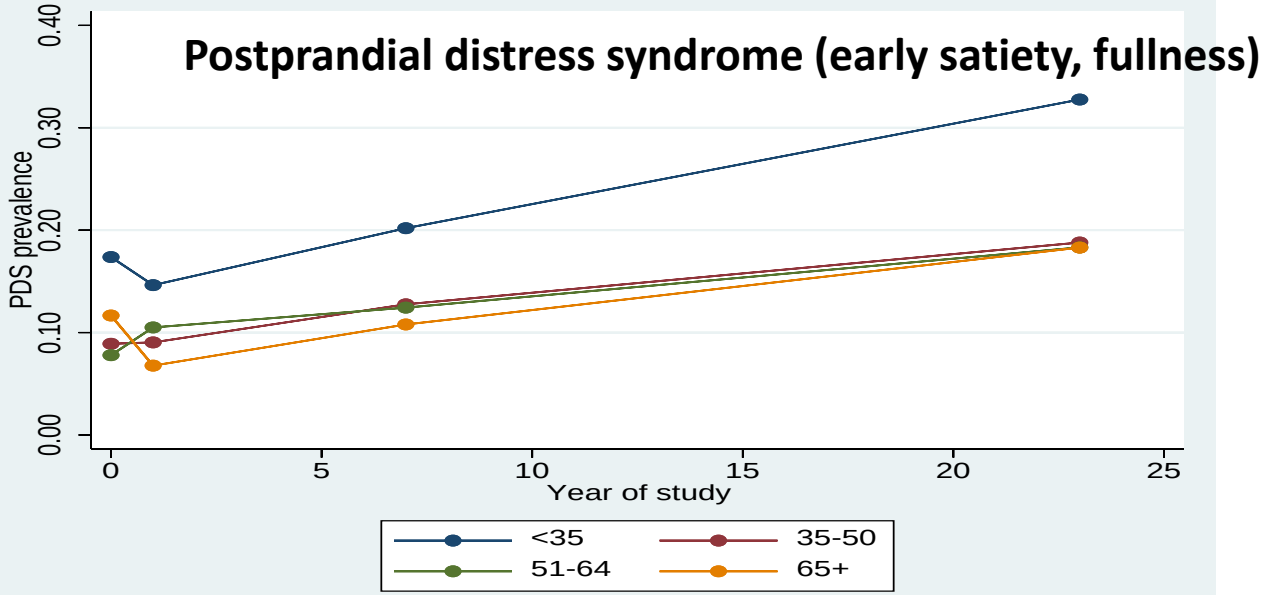
Effect of time (mixed effects logistic regression adjusting age, sex):

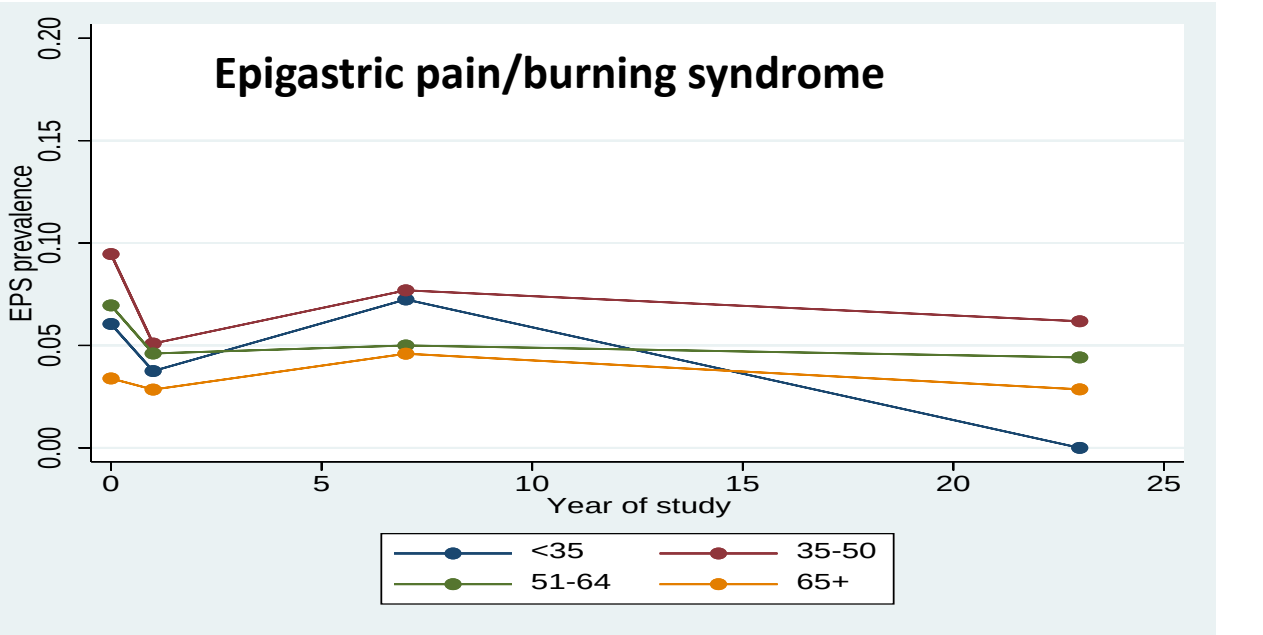
FD OR=2.24 (1.71-2.94)

PDS OR=3.51 (2.57-4.81)

EPS OR=1.5 (1.09-2.05)

Andreason, Talley et al. Am J Gastroenterol. 2020; doi: 10.14309/ajg.0000000000000972

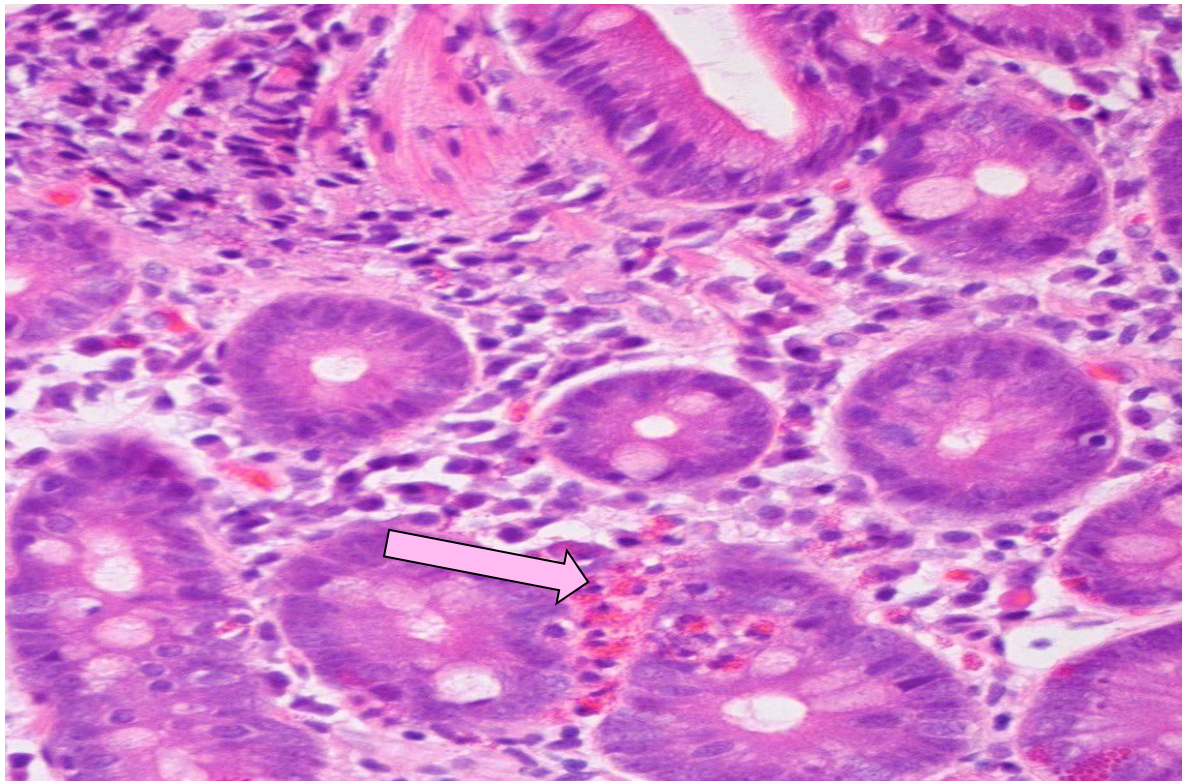




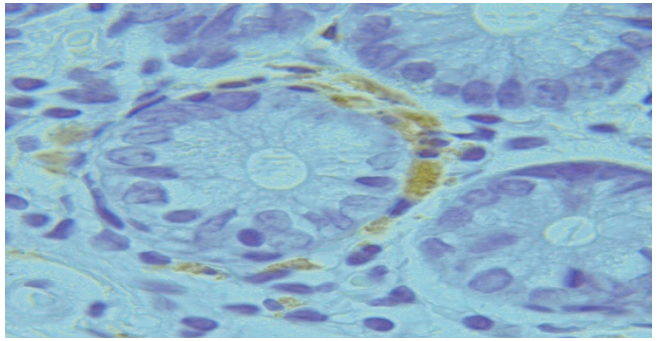
Nonulcer Dyspepsia and Duodenal Eosinophilia: An Adult Endoscopic Population-Based Case-Control Study

Clin Gastroenterol Hepatol. 2007 5:1175-83

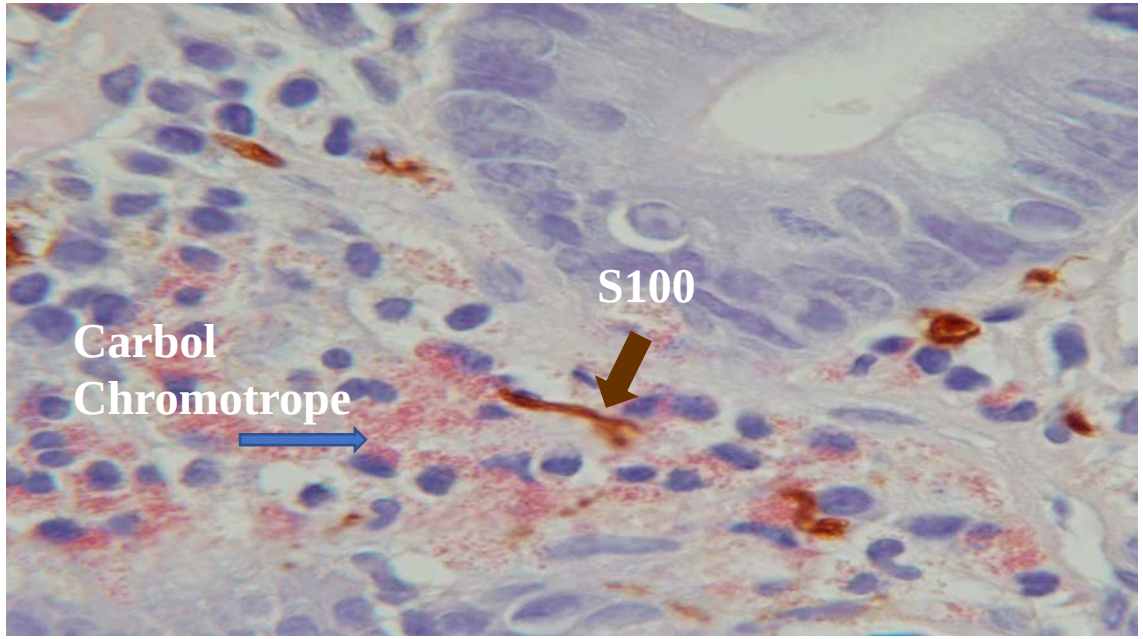
NICHOLAS J. TALLEY,*,‡ MARJORIE M. WALKER,§ PERTTI ARO,‖ JUKKA RONKAINEN,‖ TOM STORSKRUBB,‖ LAURA A. HINDLEY,§ W. SCOTT HARMSEN,¶ ALAN R. ZINSMEISTER,¶ and LARS AGRÉUS‖



Clusters of eosinophils in D1 observed in 26 FD (51%) vs. 10 controls (21%) (p=0.003)

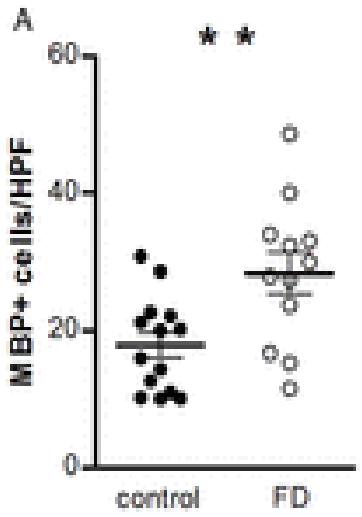


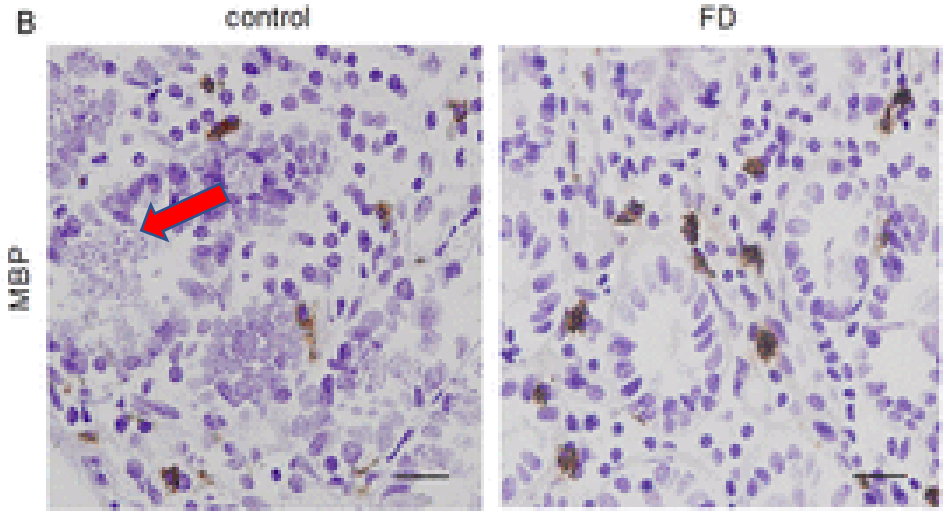
MBP – degranulation in FD may be key…

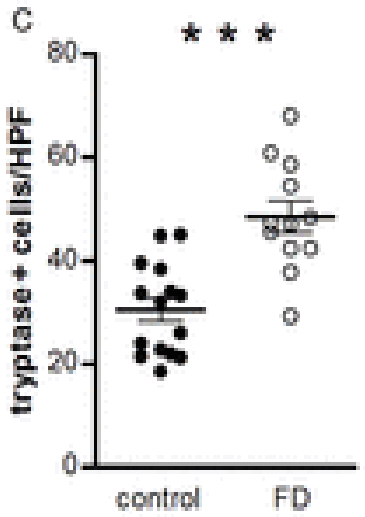


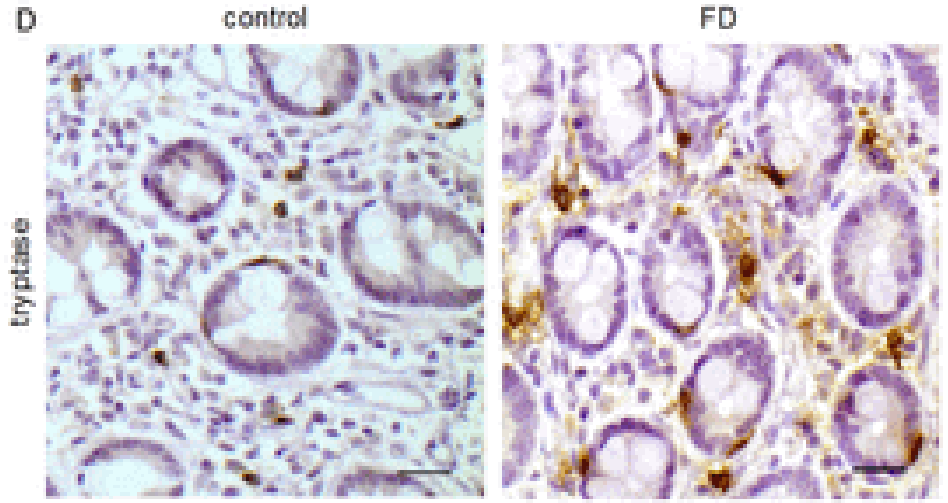
PDS <u>not</u> EPS linked to duodenal eosinophils

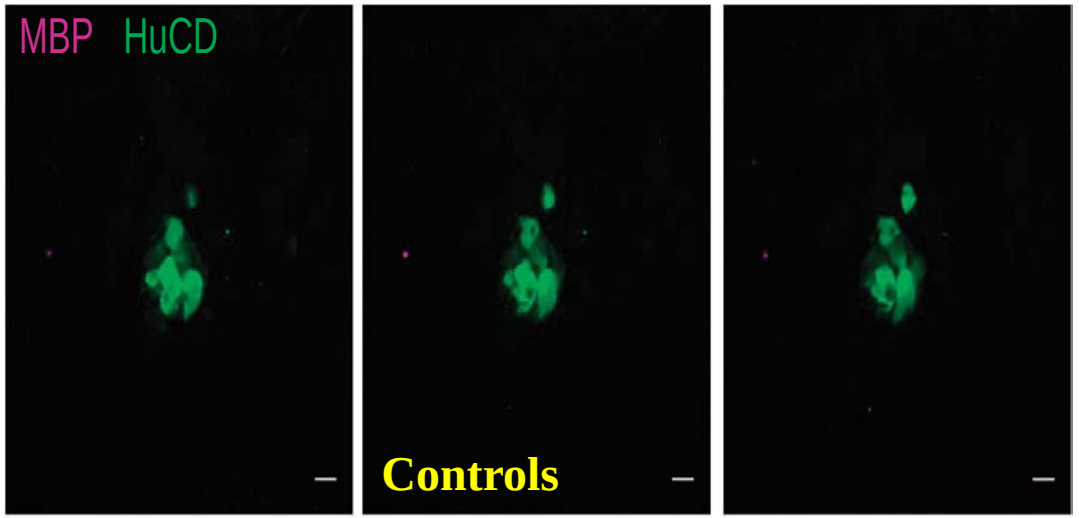
Independent verification Leuven: increased permeability, altered neuronal structure and function in FD ±IBS

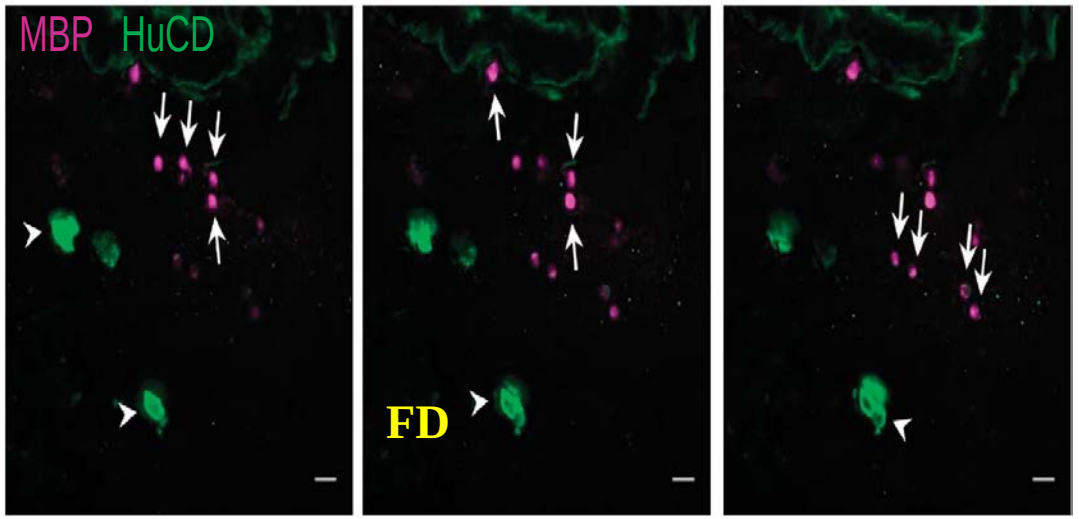








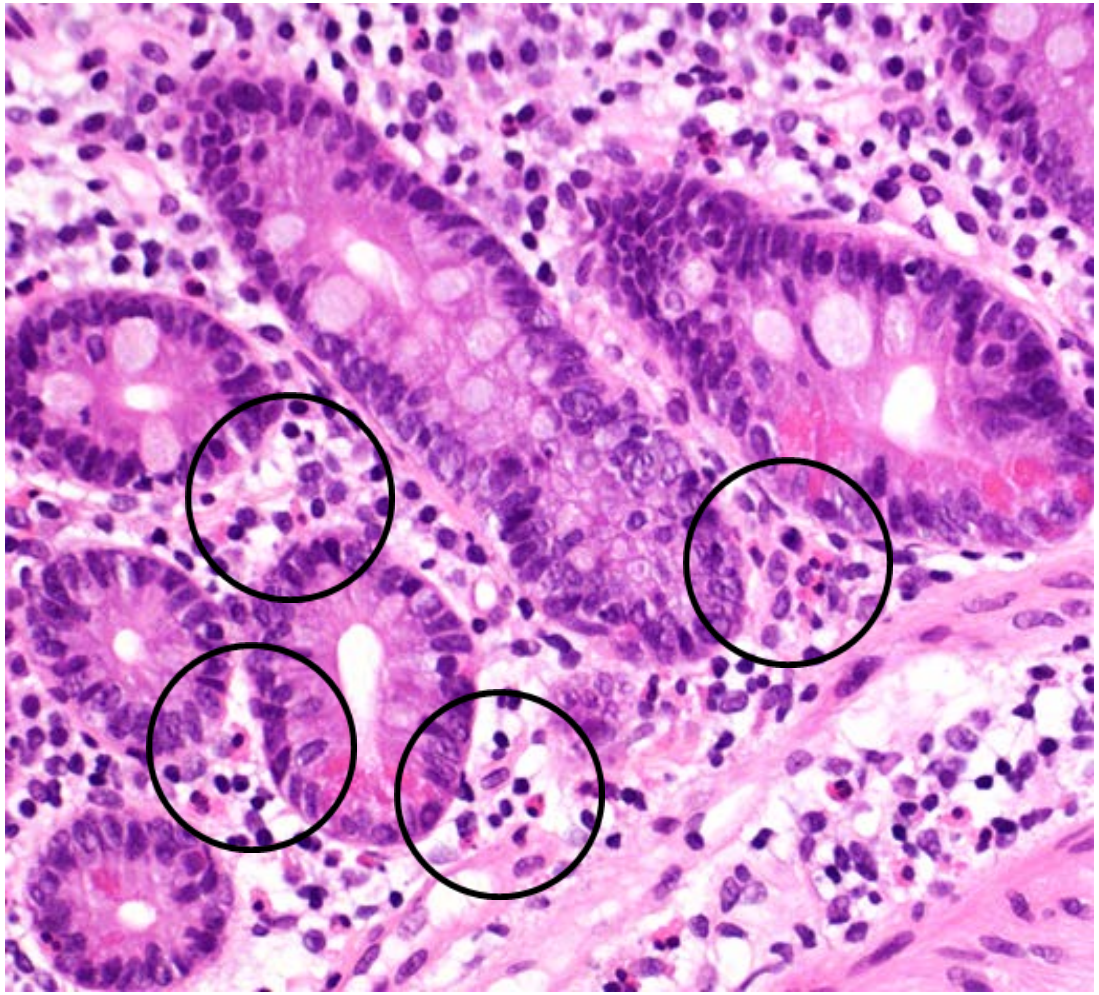




Duodenal eosinophils in FD (n= 15 cases vs. 15 controls)

Cirillo et al. Am J Gastroenterol 2015;110:1205-15

Duodenal eosinophils a biomarker for non-celiac wheat sensitivity (controversial!)



Diagnosis by double-blind wheat challenge

- Duodenal eosinophilia (circled) in NCWS
- NCWS overlaps with IBS/FD in at least 50% cases
- Increased rectal eosinophils also observed

Carroccio *et* al Am J Gastroenterol 2012; 107:1898–1906
Carroccio et al. Clin Gastroenterol Hep 2018

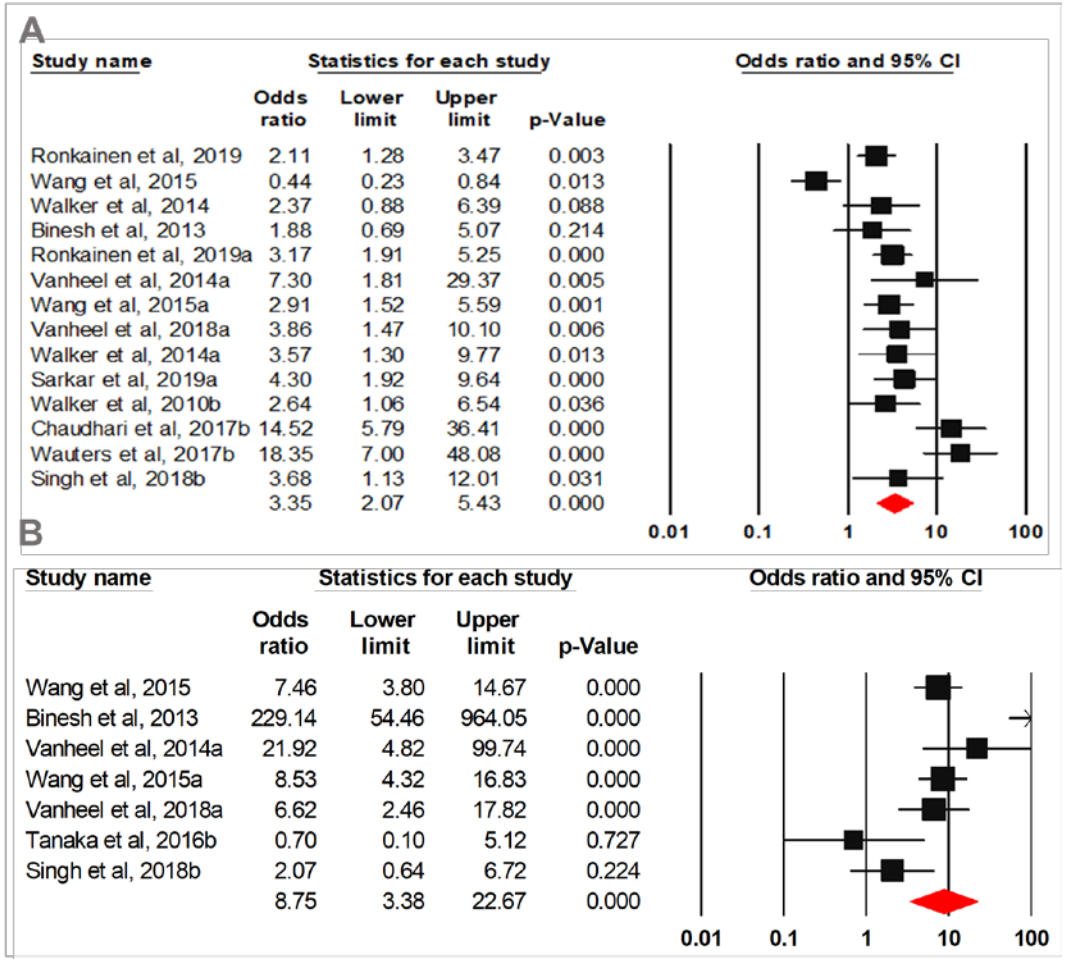
- ? Innate immune system involvement
  - Increased intestinal permeability
  - Epithelial cell damage
  - Duodenal (and rectal) eosinophilia?

Gastroduodenal eosinophilia and mast cells in functional gastrointestinal disorders: a meta-analysis

Summary of meta-analysis results of cell counts between patients and controls by disease group and anatomical location

Study category	N studies	OR	95% CI, p value	Mean difference	95% CI, p value
FD					
Eosinophils, gastric antrum	**2**	**7.76**	**3.19-18.92, p<0.001**	**7.09**	**4.15-10.03, p<0.001**
Eosinophils, D1	4	1.39	0.59-3.28, p=0.458	0.58	-0.50-1.67, p=0.293
Eosinophils, D2	**6**	**3.50**	**2.57-4.77, p<0.001**	**1.73**	**0.75-2.71, p=0.001**
Eosinophils, combined duodenum	14	3.35	2.07-5.43, p<0.001	2.28	1.32-3.25, p<0.001
Mast cells, gastric antrum	**5**	**2.13**	**1.38-3.28, p=0.001**	**3.01**	**1.36-4.66, p<0.001**
Mast cells, D1	**2**	**38.90**	**1.36-1112.82, p=0.03**	**3.87**	**3.26-4.49, p<0.001**
Mast cells, D2	**3**	**8.90**	**5.26-15.05, P<0.001**	**15.54**	**0.99-30.09, P=0.03**
Mast cells, combined duodenum	7	8.75	3.38-22.67, P<0.001	4.22	2.55-6.89, P<0.001
IBS					
Eosinophils, D2	2	0.24	0.01-10.81, p=0.429	-1.23	-5.26-2.79, p=0.548
Mast cells, D2	2	1.87	0.44-7.93, p=0.394	2.10	-2.82-7.02, p=0.403
FD/IBS					
Eosinophils, gastric antrum	**4**	**2.45**	**1.51-3.98, p<0.001**	**1.41**	**0.25-2.58, p=0.017**
Eosinophils, gastric corpus	5	1.94	0.97-3.85, p=0.059	0.61	-0.04-1.25, p=0.066
Eosinophils, combined gastric	9	2.13	1.41-3.20, p<0.001	0.89	0.28-1.50, p=0.004
Eosinophils, D1	4	2.19	0.96-5.01, p=0.063	1.46	-0.19-3.10, p=0.082
Eosinophils, D2	5	2.19	1.03-4.67, p=0.042	1.59	-0.14-3.33, p=0.072
Eosinophils, combined duodenum	12	2.27	1.53-3.37, p<0.001	1.83	0.74-2.91, p=0.001
Mast cells, D2	2	3.81	1.17-12.46, p=0.027	8.94	-4.43-22.31, p=0.190
Mast cells, combined duodenum	5	2.62	1.43-4.79, p=0.002	4.56	1.02-8.10, p=0.012

Duodenal eosinophils and mast cells in functional dyspepsia vs. controls



Brown et al, DDW Virtual 2021, poster presentation

Eosinophilic duodenitis and GERD

Change of PDS to GERD	OR	95% CI
Eosinophilia in D1, crude*	1.6	0.50-4.84
Eosinophilia in D1, adjusted	1.8	0.52-6.06
Eosinophilia in D2, crude*	4.1	1.19-14.0
Eosinophilia in D2, adjusted**	6.3	1.50-26.37

PDS to incident GERD symptoms over 10 years:
OR 8.8, 95% CI 3.4-22.9

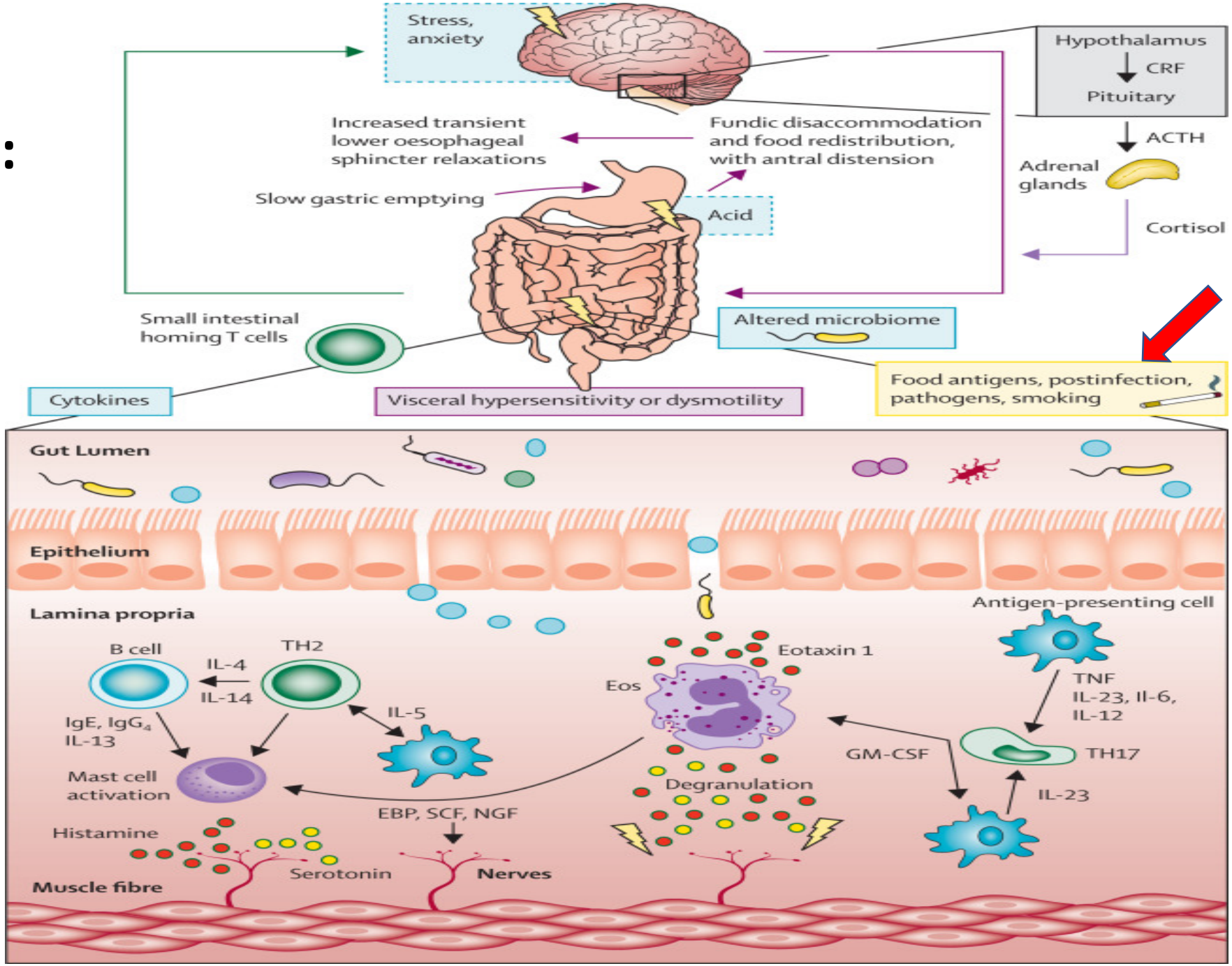
EPS OR 2.3, 0.56-9.24

Ronkainen J, Talley NJ et al. Aliment Pharmacol Ther. 2019; 50: 24-32

Age dichotomized at 60 years, *H. pylori* positive by histology or culture.
*Adjusting for age and sex only
**Variables in the final model: *age*, *gender*, *use of proton pump inhibitors (PPIs)*, *smoking (yes/no)*, *H. pylori infection* and *anxiety*.

Duodenal eosinophilia (D2) was associated with a 6-fold increased risk of NEW ONSET symptomatic GERD at 10 year follow-up in FD-PDS (but not EPS)

DBGIs (FGIDs) and immune activation: disease model



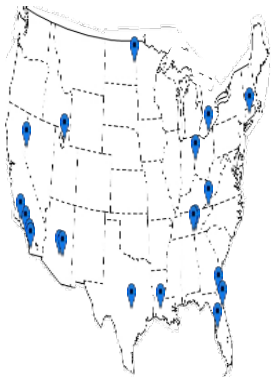
Talley NJ, Ford AC. N Engl J Med 2015;373: 1853-63

Talley NJ. Am J Gastroenterol. 2020; 115: 41-48

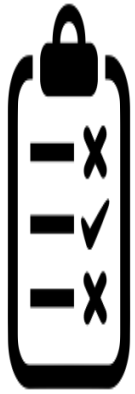
Ford AC, Mahadeva S, Carbone MF, Lacy BE, Talley NJ. Lancet. 2020;S0140-6736(20)30469-4.

DDW 2021 Talley et al.

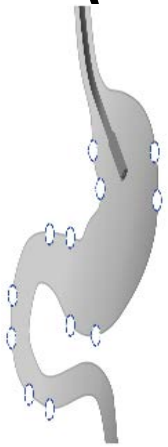
Landmark: US Gastroduodenal Eosinophil Discovery Rate in Chronic Unexplained (Functional) GI Symptoms



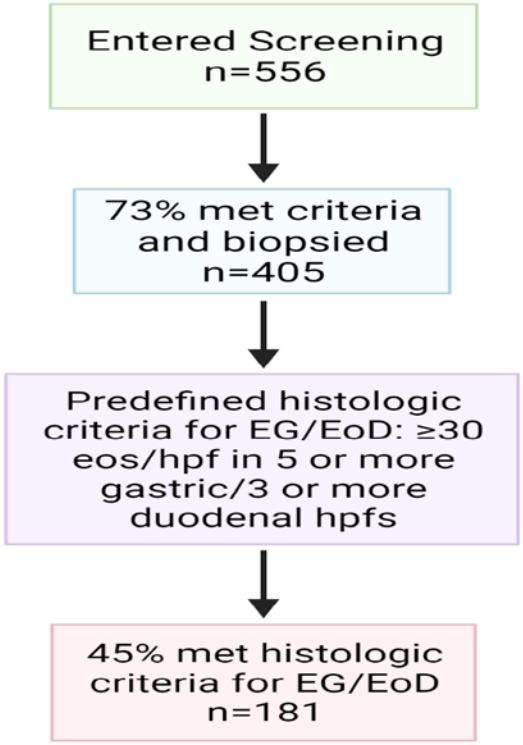
500+ patients screened and evaluated **across 20 sites**, with 400+ undergoing endoscopy

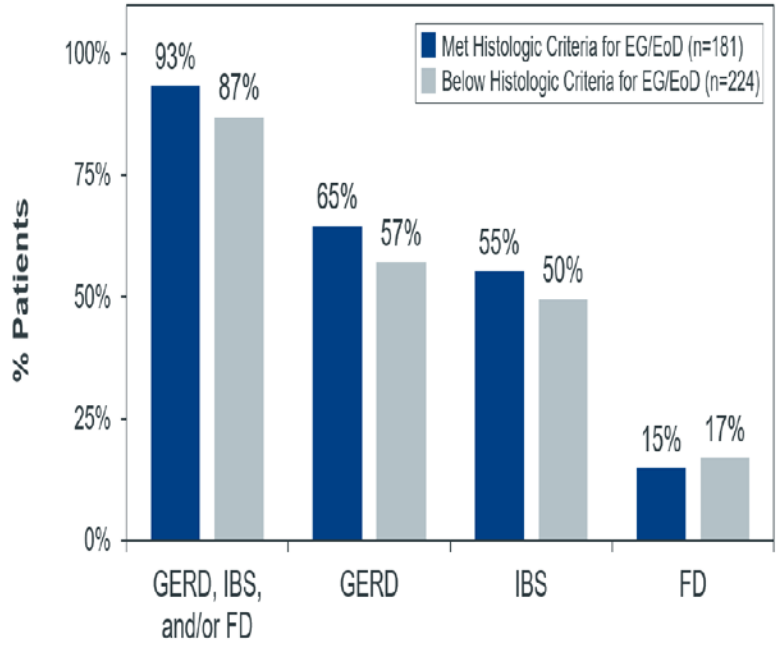


PRO measured a broad constellation of symptoms and identified **moderate-to-severe** symptomatic patients



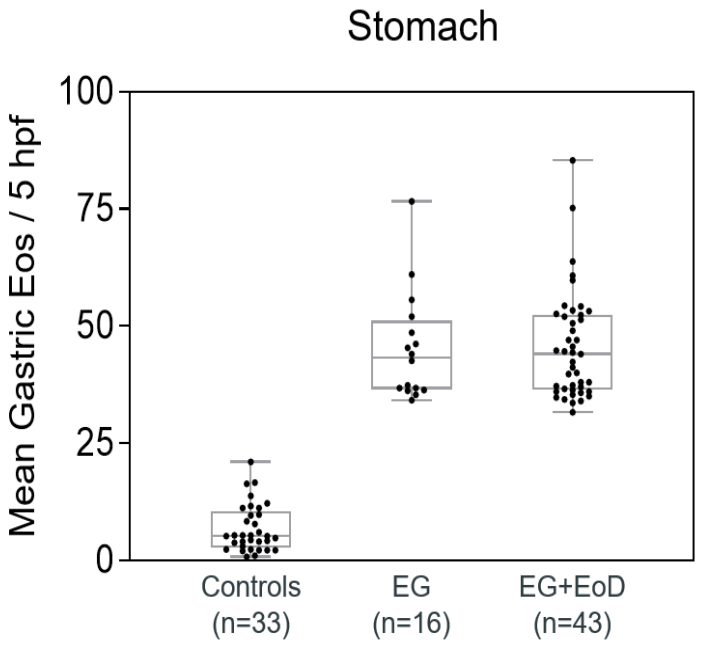
Standardized **endoscopy and biopsy** protocol with pre-defined criteria for eosinophilia (and mast cells)

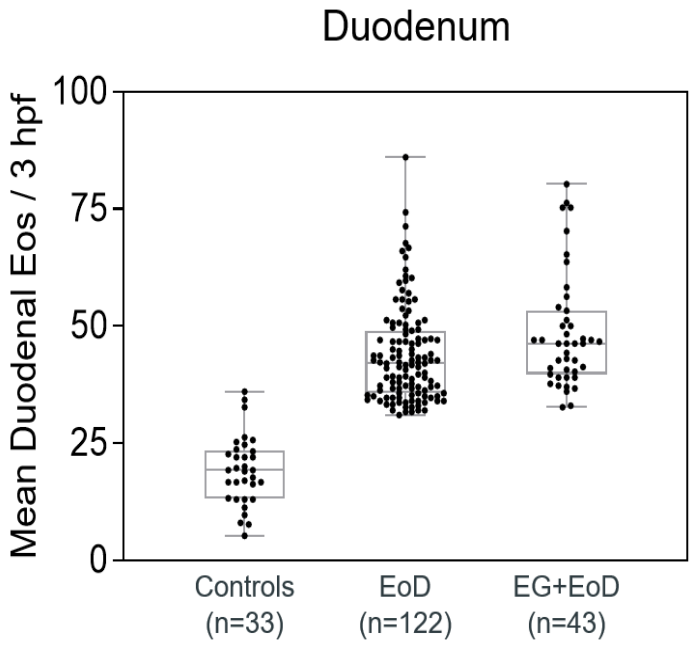


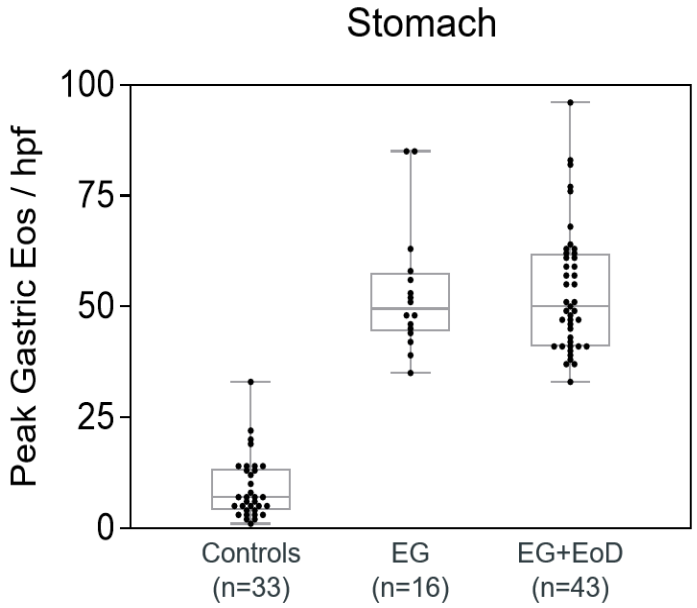


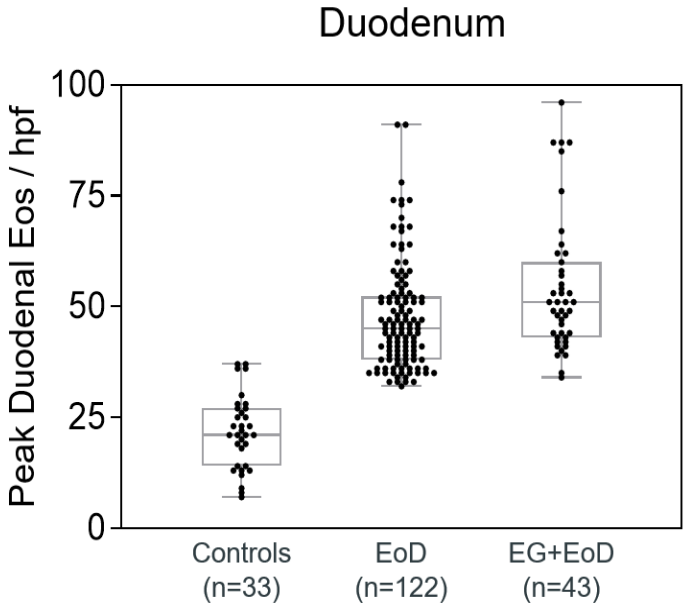
- **First large prospective** study looking at discovery rate of eosinophilic duodenitis (EoD)/gastritis (EG) globally
- Study population **highly representative** of typical community GI practice seeing chronic (functional) GI symptoms
- >90% patients had a diagnostic label of IBS, GERD or functional dyspepsia pre-study (and pre-endoscopy/biopsy)
- **Consistent findings** across U.S. geographical locations
- **Eosinophils and mast cells** both significantly **increased** in symptomatic patients

Mean and Peak Eosinophils Counts in Stomach and Duodenum of Patients Meeting Histologic Criteria for EG/EoD and Controls



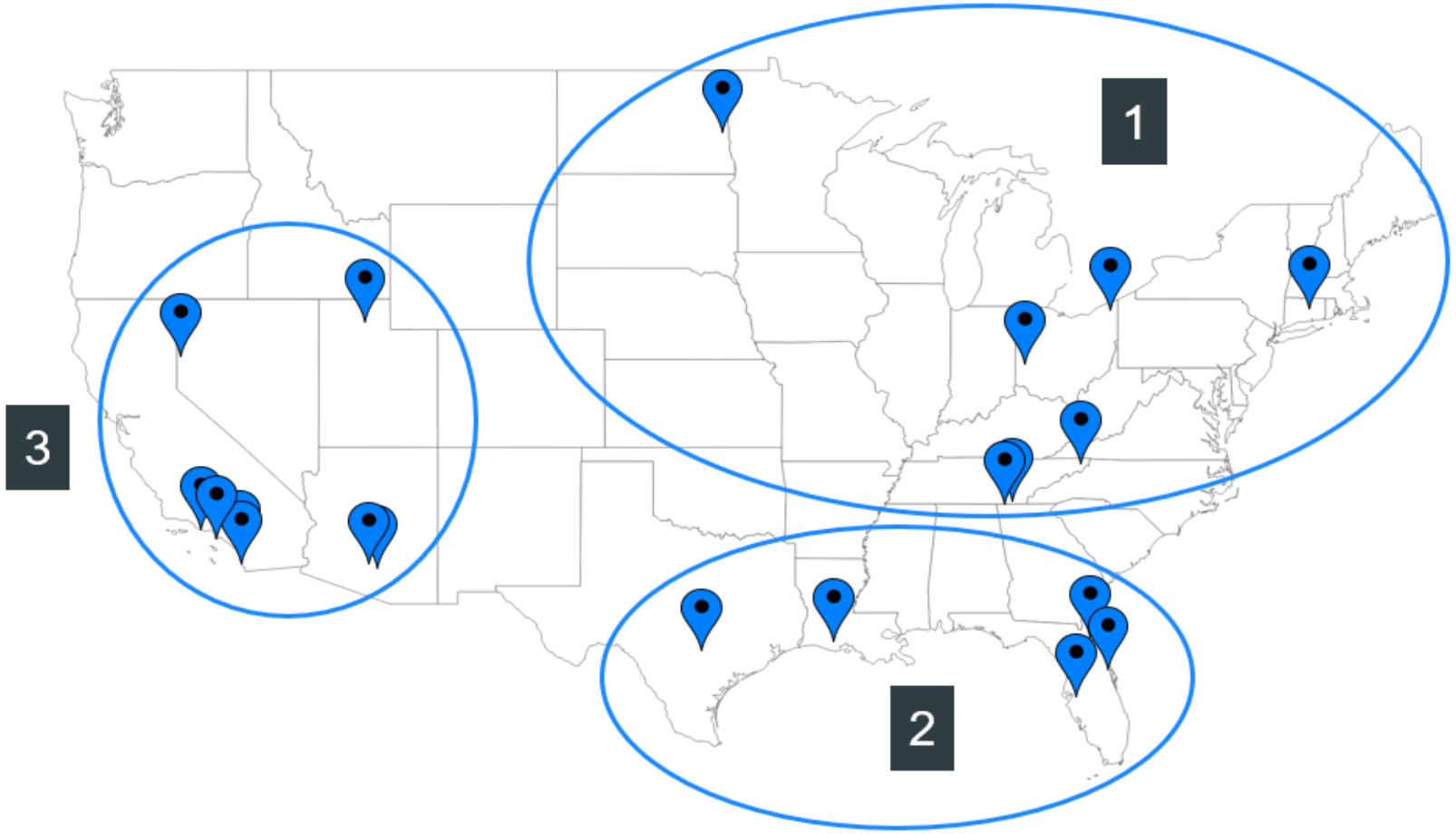






Mean (A-B) and peak (C-D) eosinophil counts in stomach and duodenum of patients meeting histologic criteria for EG/EoD (≥30 eos/hpf in 5 gastric and/or 3 duodenal hpfs, respectively) compared to controls. Two controls met histologic criteria for EoD, none met EG criteria. Caps indicate min and max; box, 25th–75th percentile; center line, median.

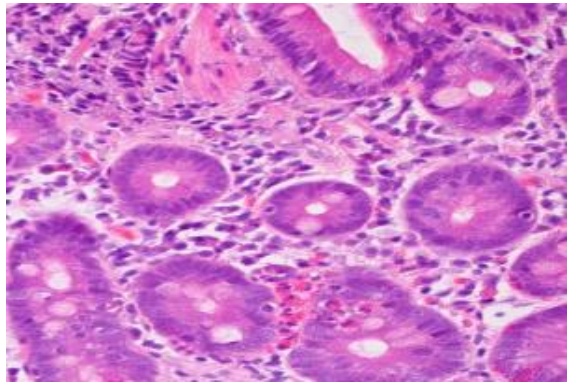
EG/EoD Discovery Rate by Region in the USA

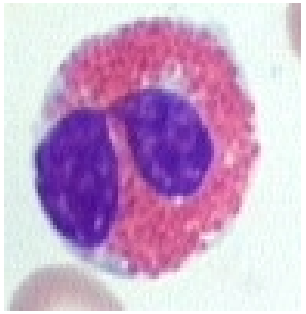


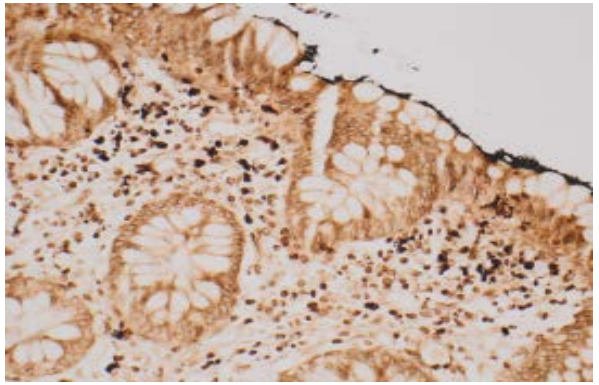
Region	# Sites	Total Patients	EG/EoD Pts	EG/EoD Rate
1	7	131	66	50%
2	5	123	60	49%
3	8	151	55	36%

Eosinophilic GI Diseases (EGIDs)

- ✓Eosinophilic duodenitis/gastritis: likely underdiagnosed – biopsy!!!
- ✓Functional dyspepsia (FD) and FD/IBS overlap – eosinophilic duodenitis (at least 40%)
  - ❖FD increasing – biopsy!
- oColonic spirochetosis, colonic eosinophilia and IBS-diarrhea
- oEosinophilic colitis (rare)
- oCoeliac disease – role of eosinophils?
- oCrohn's disease – role of eosinophils?







Eosinophilic GI diseases (EGIDs)

Likely under-diagnosed:

- Eosinophilic esophagitis (EoE)
- Eosinophilic duodenitis (EoD) and functional dyspepsia, IBS, GERD
- Eosinophilic gastritis (EG) and FGIDs
- Colonic spirochetes and IBS diarrhea (colonic eosinophilia)

Walker MM, Potter M, Talley NJ. *Lancet Gastroenterol Hepatol.* 2018;3(4):271-280.

Thank you!

Australian Gastrointestinal Research Alliance

NHMRC Centre of Research Excellence in Digestive Health 2019-2024

Australia
Neurogastroenterology: Nick Talley (UoN), Gerald Holtmann (UQ)
Anatomical Pathology: Marjorie Walker (UON) Nicola Wood (Adelaide)
Mucosal Immunology GI group: Simon Keely (UoN), Grace Burns (UoN)
Microbiology: Mark Morrison (UQ)
Biostatistics and Psychology: Mike Jones (Macquarie University)
Psychology UQ & UoN: Natasha Koloski
Pharmacy and Experimental Pharmacology: Susan Hua (UoN) - nanotechnology
Gastroenterology: Michael Potter, Tom Goodsall, Alkesh Zala, Mudar Irani

International

- **Sweden, Karolinska Institutet and Finland, University of Oulu** Anna Andreasson, Linn Inganäs , Lars Engstrand, Henry Nyhlin, Lars Kjellstrom, Åke Ost, Lars Agréus, Peter T. Schmidt, Pertti Aro, Jukka Ronkainen
- **Mucosal Immunology Group Imperial London** Nick Powell
- **Mayo Clinic** Yuri Saito, Joe Murray
- **Leeds, UK** Alex Ford
- **Leuven Belgium** Jan Tack Tim Vanuytsel Lucas Van Oudenhove Lucas Wauters
- **Baylor Texas, USA** Ellionore Jarbrink

BREAK – 10 MINUTES

PANEL DISCUSSION AND Q&A

LUNCH – 55 MINUTES

SESSION 2- ASSESSING CLINICAL BENEFIT IN EGID

Life With an EGID & Goals of Treatment

History

- I first got sick back in 2013 with severe anemia
- A year later, in 2014 I was diagnosed with Eosinophilic Gastritis

Major Surgeries/ Hospitalizations:

- November 2014- first perforation (emergency surgery)
- May 2015- upper gastrointestinal bleed
- March 2016- partial gastrectomy
- October 2016- upper gastrointestinal bleed
- October 2018- second perforation (emergency surgery)
- February 2019- contained perforation

History

- In January of 2016 I went on the elemental diet with a NG tube to determine if my condition was food dependent or not.
- I tried so many different medications such as budesonide, prilosec, protonix, mercaptopurine, and prednisone.
- The prednisone never really showed signs of working when I was on it but when I tried to come off of it my symptoms increased.
- The mercaptopurine really only was beneficial at a higher dose (100mg) but at that high dosage, my liver was being affected.

Most Troublesome Symptoms

The biggest, most debilitating symptom is the constant stomach pain after meals especially.

- Along with the stomach pain, I also experience radiating pain into my left shoulder which often causes pain when I walk and breathe.
- Nausea
- Anemia was another troublesome symptom I had

➔ I was constantly tired and weak which made softball and school more challenging.

Quality of Life

- I missed over 100 days of high school because of being too sick to be at school or due to hospitalizations
- My social relationship with food was very poor. I planned my eating around when I would be out doing things or with family and friends so I would be in less pain
- Eating was not enjoyable to me because everything I ate or drank gave me debilitating pain
- I missed out on many of the high school experiences because I was either too sick or in the hospital
- I had less playing time because again, I was too sick or in the hospital

Day to Day Life

- For 6 years there wasn't a day that I wasn't in pain at some point in the day
- I had a select few foods that I ate and would cause limited pain
- During the school year I would typically make it through the first half of the day but I usually left after lunch because the pain was too bad
- I had to strategically make my schedule so I had a later lunch with less classes after lunch… the ones I did have were typically the easier classes.
- I tried to keep my life as normal as possible, I didn't let my disease define me and not a lot of people knew I was sick because I hid it so well

Day to Day Life

- Freshman year of high school I knew I wanted to go into nursing so I followed a science heavy course load the remaining years of school
- Since I spent so much time in the hospital I was constantly playing catch up, at times I was failing most if not all my classes.
- Senior year I started doing my catch up work while still admitted to the hospital
- Despite missing 100+ days and I finished high school with a 3.2 GPA and am going into my third year of college with a 3.7 GPA, my CNA license and one more prerequisite until I apply to the nursing program.

Ideal Treatment

- Finding one medication that could combat all my symptoms of EG would be ideal so I didn't have to take four different medications for all my different symptoms
- A medication or treatment that doesn't have too many major side effects

Goals of Treatment

- Obviously the biggest goal for any treatment is to improve quality of life… so that is the main goal I would like to see come from a treatment
- On a smaller, more day to day scope of things, I would like to be able to eat and enjoy the food I put into my body rather than dreading what will happen after, have energy, and have limited nausea throughout the day
- A consistent treatment- meaning my body won't become tolerant to it or that it won't randomly just stop working. Granted, nothing is guaranteed but many of the medications I have tried have worked for a year or so and then they stopped being beneficial.

Defining Clinical Benefit in Clinical Trials for EGID: An FDA Perspective

Sarrit Kovacs, PhD

Division of Gastroenterology (DG)
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research, FDA

Disclosure Statement

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the speaker and should not be construed to represent FDA's views or policies
- In this talk "drug" refers to both drugs and biologic therapies

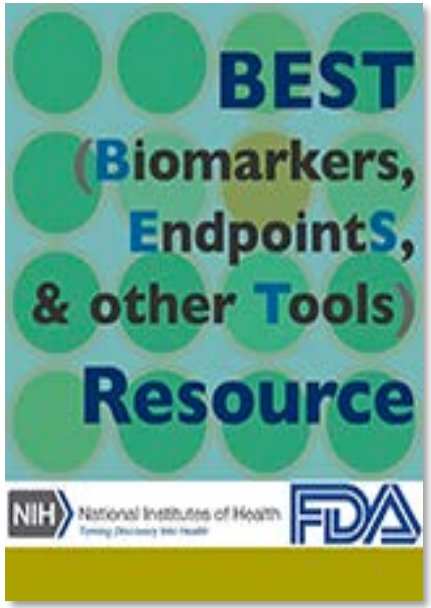
Overview

- Regulatory Definition of Clinical Benefit
- Leveraging the EoE Approach
  - Clinicopathologic Assessment
    - Histologic Improvement
    - Symptomatic Improvement
- Opportunities for Advancement in EGIDs

Regulatory Definition of Clinical Benefit

- FDA-NIH BEST glossary definition of “clinical benefit”:
  - A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives.

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care



FDA-NIH Biomarker Working Group BEST Resource glossary:
https://www.ncbi.nlm.nih.gov/books/NBK338448/

Clinical Benefit: Evidentiary Standard

- Regulatory Requirement:
  - Demonstrate **substantial evidence of effectiveness** [1] (i.e., clinical benefit)
- Substantial evidence is defined as evidence consisting of ***adequate and well-controlled investigations*** [2]
  - Usual approval standard is two adequate and well-controlled studies (affirm and confirm)
  - Drug development program has been designed well to be able to "distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation"

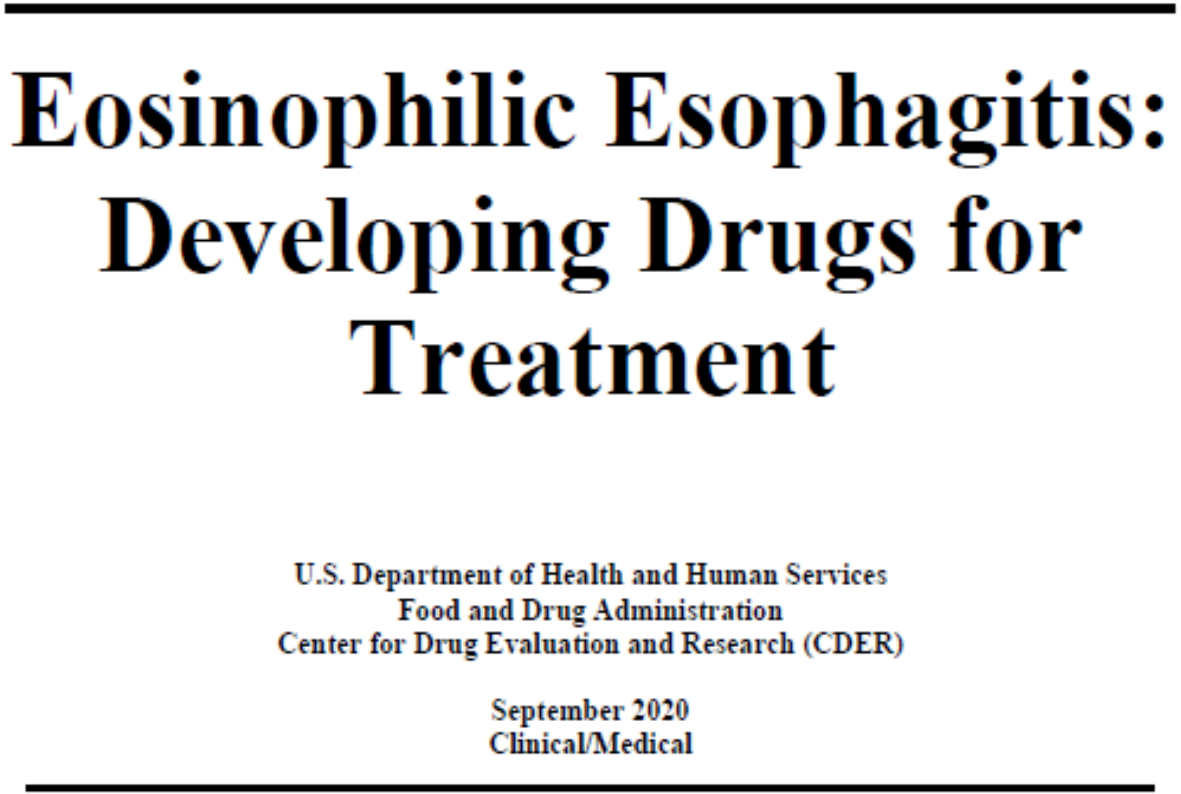
[1] 21 CFR 314.50

[2] 21 CFR 314.126

Challenges to Defining Clinical Benefit in EGIDs Beyond EoE

- Lack of clinical consensus diagnostic criteria
- Heterogeneous nomenclature
- Natural histories are not well understood/characterized
- Lack of regulatory/drug development precedent
- Rare diseases with few patients available to participate
  - Multi-center, multi-country trials
- Pediatric-specific considerations

Leveraging the EoE Approach



Eosinophilic Esophagitis: Developing Drugs for Treatment

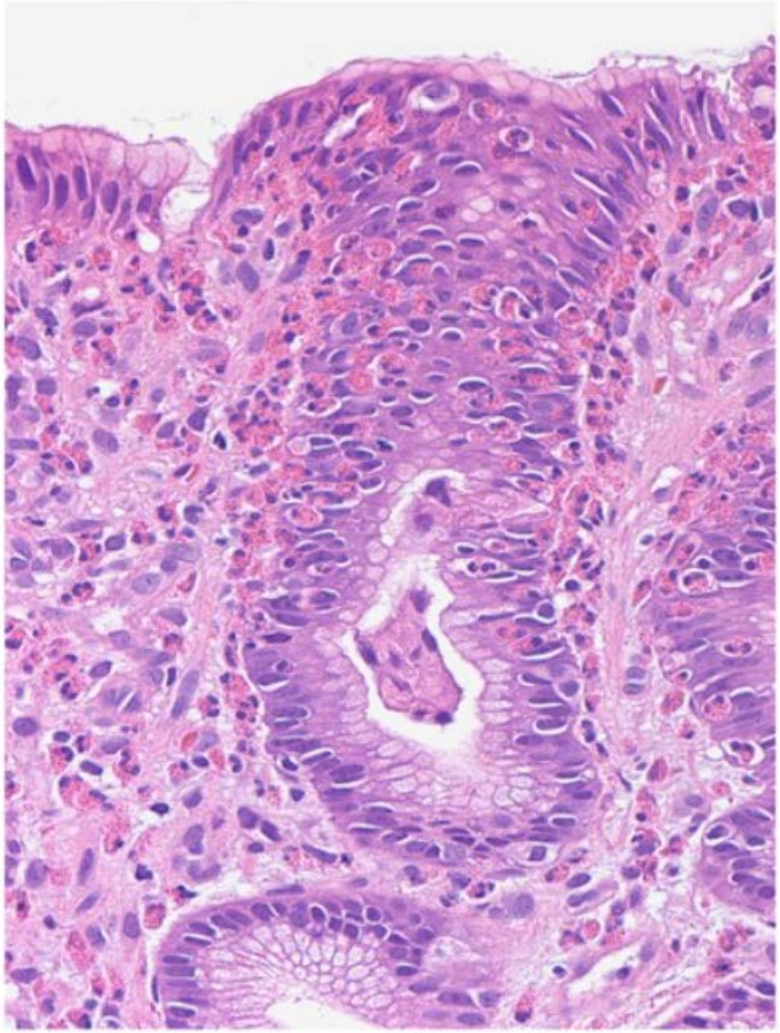
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2020
Clinical/Medical

Clinicopathologic Assessment

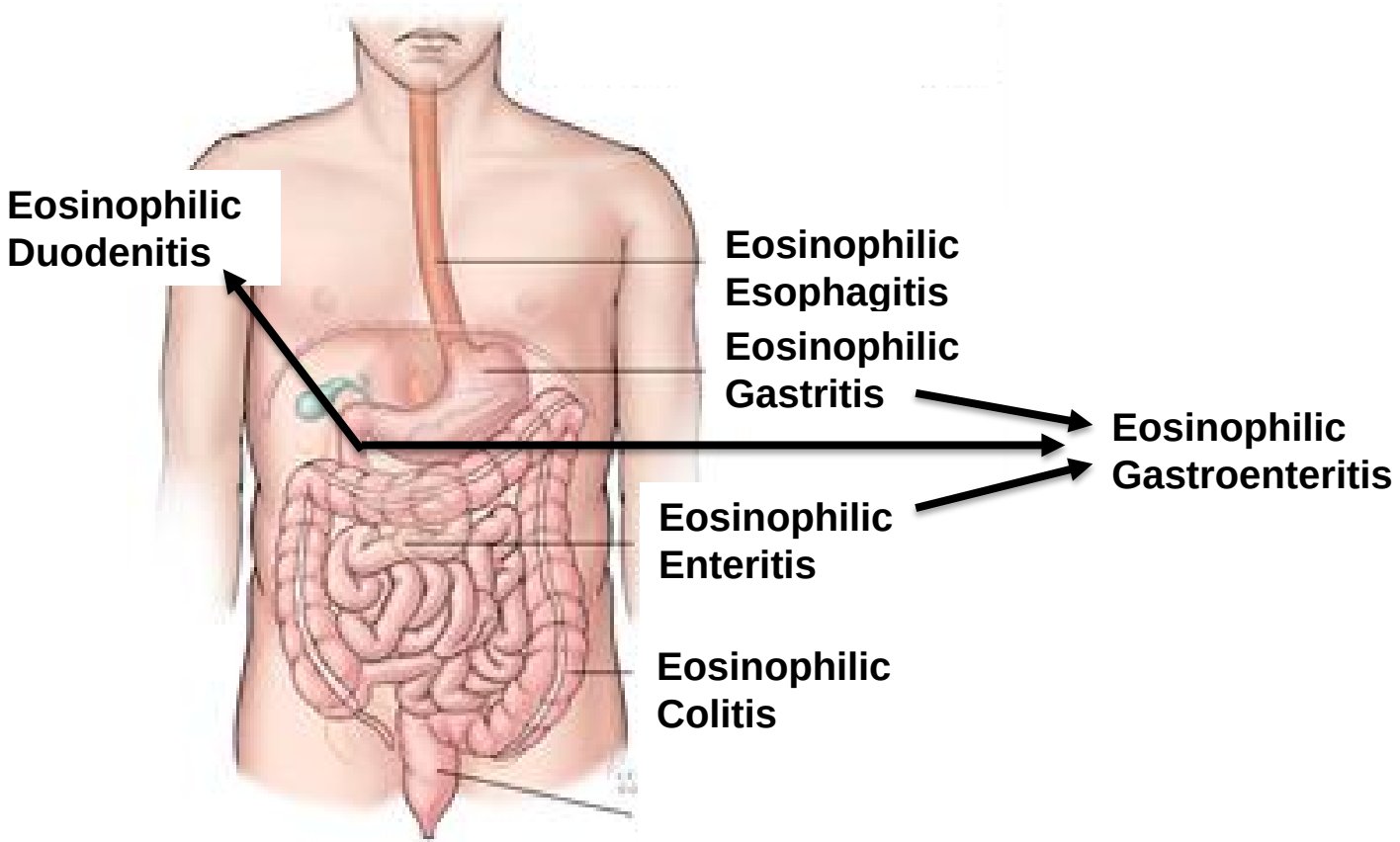
- Therapeutic goals for patients with EGIDs:
  - Favorable effect on underlying disease (e.g., normalize histology)
  - Eliminate or meaningfully decrease symptoms of active disease
- Coprimary endpoints recommended in EoE:
  - Document a histologic response based on a peak eosinophil count per high-power field (HPF) across all available biopsies
  - Assess significant improvement from baseline in signs and symptoms, compared to placebo, using a well-defined and reliable clinical outcome assessment (COA) instrument
    - Clinically meaningful effect that is considered a treatment benefit to patients

Histologic Assessment



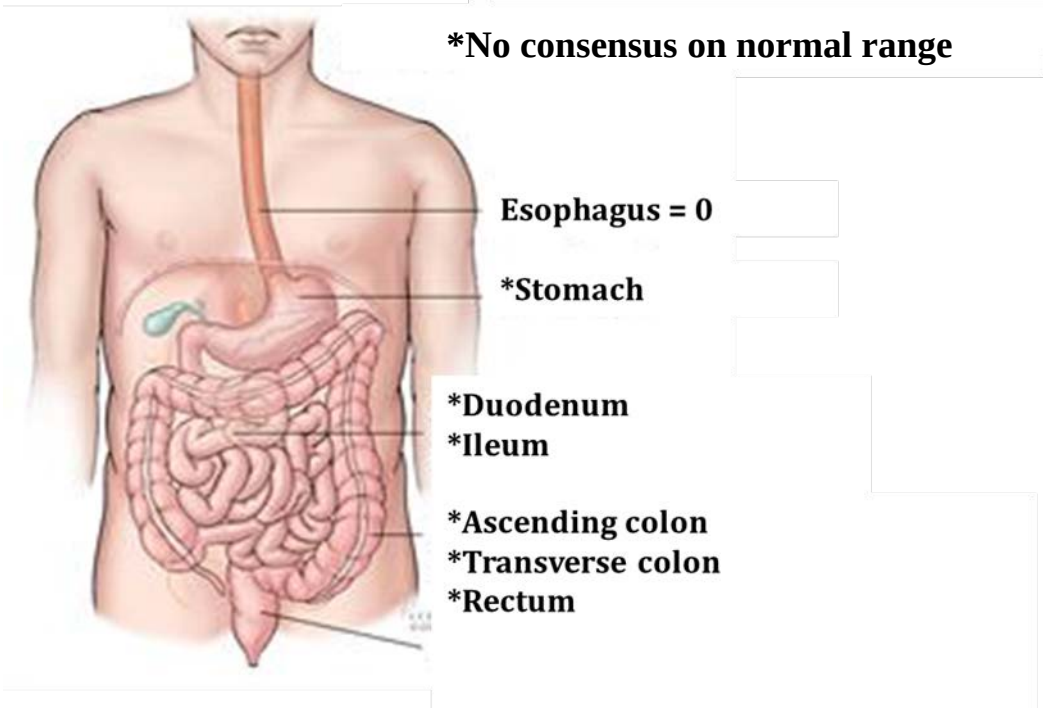
Source: Lwin T, Melton SD, & Genta RM, Modern Pathology, 2011 (https://www.nature.com/articles/modpathol2010221)

EGID Definitions



Adapted from https://my.clevelandclinic.org/health/diagnostics/4986-gastrointestinal-examinations

How many eosinophils are normal?



Adapted from https://my.clevelandclinic.org/health/diagnostics/4986-gastrointestinal-examinations

Site	#/0.27 mm^2
Antrum	<1-19
Corpus/fundus	<1-16
Stomach NOS	3-33
Duodenal bulb	Not reported
Duodenum	<1-70
Ileum	<1-92
Cecum	<1-46
Ascending colon	<1-48
Transverse colon	1-41
Descending colon	<1-25
Sigmoid	0-24
Rectum	0-31

Table adapted from Dr. Margaret Collin's 2021 EGID Workshop slide #5

What are Clinical Outcome Assessments (COAs)?

- Clinical outcome assessments (COAs) measure or describe **how a patient feels, functions, or survives**
- COAs are different from other outcome assessments, such as survival and surrogates (often times biomarkers, which are intended as a substitute for how a patient feels, functions, or survives)
- **Types of COAs include:**
  1. **Patient-reported outcome (PRO) assessments**
  2. Clinician-reported outcome (ClinRO) assessments
  3. Observer-reported outcome (ObsRO) assessments
  4. Performance outcome (PerfO) assessments

Patient-Reported Outcome (PRO) Assessments

- A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without interpretation of the patient's response by a clinician or anyone else.

- Symptoms or other **unobservable concepts known only to the patient can only be measured by PRO measures**.

  Examples:
  - Rating scales (e.g., numeric rating scale of pain intensity)
  - Counts of events (e.g., patient-completed log of emesis episodes)

Source: FDA-NIH BEST Resource Glossary (https://www.ncbi.nlm.nih.gov/books/NBK338448/)

Assessments used in clinical practice are often not suitable for regulatory purposes

- Typically do not meet FDA's Regulatory Standards (21 CFR 314.126 [b][6])
  - *Section (b)(6): The methods of assessment of subjects' response are **well-defined and reliable**. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.*
  - **Fit-for-purpose**
    - "A conclusion that the level of validation associated with a biomarker or COA is sufficient to support its proposed use." [1]

[1] FDA-NIH Biomarker Working Group BEST Resource Glossary (https://www.ncbi.nlm.nih.gov/books/NBK338448/)

Interpretability of COA Endpoint Data

- To allow for interpretable COA efficacy endpoint data, patients enrolled should be sufficiently symptomatic in order to:
  - Demonstrate a treatment effect
  - Inform a benefit-risk assessment
- A percent change from baseline endpoint, or a responder analysis endpoint, is not recommended unless the targeted response is complete resolution of signs and symptoms
- Signs and symptoms should be assessed on a continuous or ordinal scale (e.g., change from baseline in absolute score)
- Small group-level mean differences in the COA endpoint, even if statistically significant, may not establish whether the effect is clinically meaningful to patients

Determining Clinically Meaningful Change in COA Endpoint Scores

- It is helpful to propose a range of within-patient score change that patients consider to be clinically meaningful using anchor-based methods (PGIS, PGIC scales), supplemented with empirical cumulative distribution function (eCDF) curves using data pooled across trial arms.
- Additionally, a supportive graph (i.e., eCDF) of within-patient change from baseline by treatment arms is beneficial to determine whether there appears to be a treatment difference within the range representing a meaningful improvement to patients.
- These analyses promote the detection and characterization of clinically meaningful change and facilitate interpretation of results across drug development programs.
- Ideally, these analyses are conducted prospectively using data from early stages of drug development (prior to phase 3).

Patient Considerations when Collecting COA Data

- When heterogeneity in disease symptoms/signs exists, consider defining the COA endpoint based on symptoms/signs that are most widely-characterized and most common and meaningful to the patients of interest, which are expected to improve or stabilize with treatment
- The COA's recall period, response options, and administration schedule should be based on patient input regarding how they experience their symptoms (i.e., episodic/chronic, frequency/severity)
- Decrease patient burden – consider frequency of site visits needed to develop novel COAs, identify the optimal number of COAs to include in a clinical trial
  - Avoid duplication of COA concepts to minimize the risk of missing data; administer in order of importance

Lyons E, Kovacs S, Kowalik M, Lee J. Importance of the patient voice in drug development: Eosinophilic esophagitis as a case example. DIA Global Forum, May 2021 (https://globalforum.diaglobal.org/issue/may-2021/importance-of-the-patient-voice-in-drug-development-eosinophilic-esophagitis-as-a-case-example/).

Dashiell-Aje E, Kovacs S. Opportunities: A regulatory perspective on the development of suitable clinical outcome assessments (COAs) for rare diseases. DIA Global Forum, August 2018 (https://globalforum.diaglobal.org/issue/august-2018/opportunities-a-regulatory-perspective-on-the-development-of-suitable-clinical-outcome-assessments-coas-for-rare-diseases/).

Pediatric Considerations when Collecting COA Data

- Collect PRO data on symptoms and functioning from pediatric patients who can reliably and validly self-report[1,2]
- Collect ObsRO data on observable signs, behaviors, and verbalizations related to the child regarding how they are feeling and functioning, if child cannot self-report.
  - It is ideal to obtain important PRO data, even from young children using simpler concepts and format (e.g., pictorial pain scale)
- Avoid proxy measures (caregivers reporting as if they are the child); the patient is the only one who can report on their unobservable symptoms (e.g., abdominal pain, nausea).

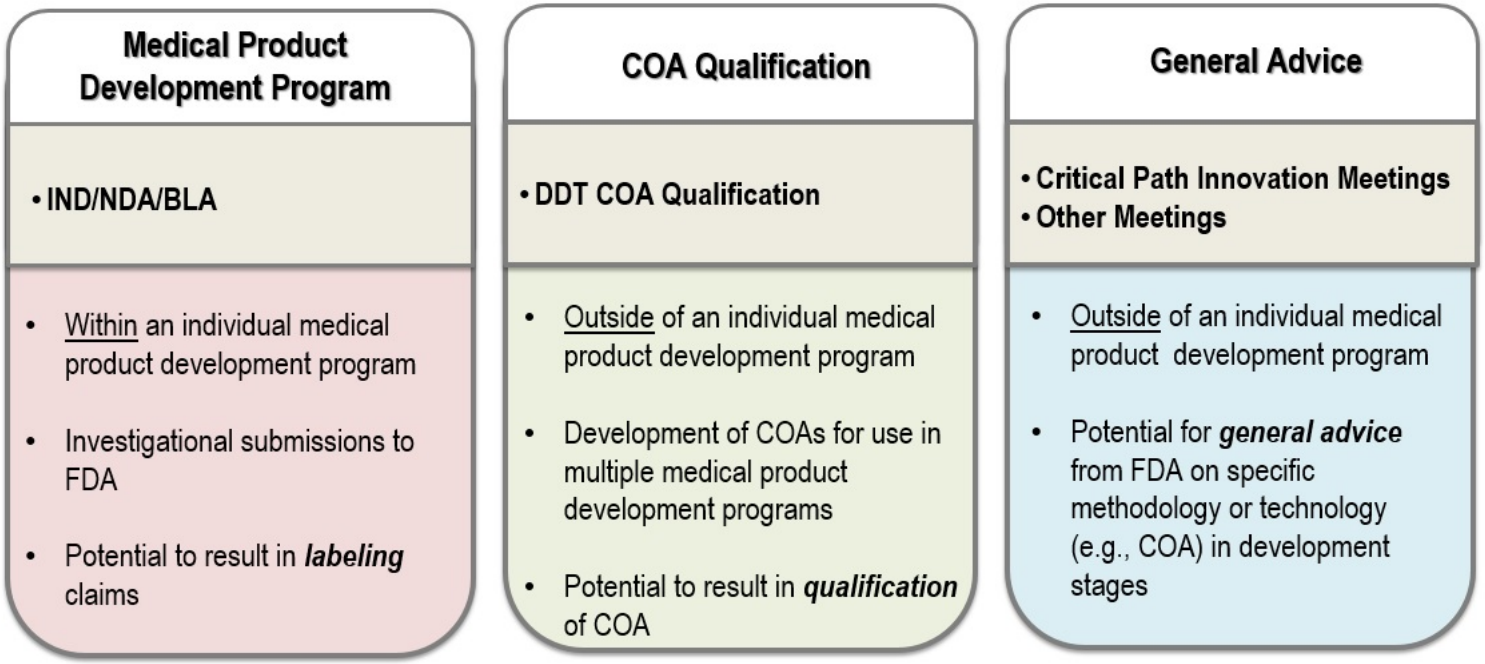
[1] Papadopoulos EJ, Patrick DL, Tassinari MS, et al. Clinical outcome assessments for clinical trials in children. In: Mulberg AE, Murphy D, Dunne J, Mathis LL, eds. Pediatric Drug Development: Concepts and Applications. 2nd ed. John Wiley & Sons, Ltd.; 2013: 539-548.

[2] Matza LS, Patrick DL, Riley AW, Alexander JJ, Rajmil L, Pleil AM, Bullinger M. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. Value Health. 2013 Jun;16(4):461-79.

Opportunities for Advancement in EGIDs

- Collaboration with patients, patient advocates, researchers, clinicians, industry, regulatory agencies, and other stakeholders
- Establish clinical consensus nomenclature and diagnostic criteria
- Further characterize the natural history for these disorders
- Use innovation, judgment, and regulatory flexibility, which are all critical in facilitating drug development for rare diseases such as EGIDs
- Frequent and early interaction with FDA during drug development

Pathways for Partnership to Facilitate Drug Development



BLA = Biologics Licensing Application; **COA =** Clinical Outcome Assessment; **DDT =** Drug Development Tool; **IND =** Investigational New Drug; **NDA =** New Drug Application

Helpful FDA Links

- Formal meetings between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf
- Division of Clinical Outcome Assessment Website: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm#Endpoints
- PRO Guidance for Industry (2009): http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
- Rare Disease Guidance for Industry:
  - Common issues: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-common-issues-drug-development-guidance-industry
  - Natural history studies: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development
- COA Qualification Website: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/clinical-outcome-assessment-coa-qualification-program
- COA Qualification Guidance for Industry: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf
- Critical Path Innovation Meetings: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm
- FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical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U.S. FOOD & DRUG
ADMINISTRATION

Clinician perspective on the assessment of meaningful benefit: adults

Kathryn Peterson MD, Msci

Eosinophilic jejunitis presenting as intractable abdominal pain. Case Rep Gastroenterol
. 2014 Dec 4;8(3):377-80

Eosinophilic gastroenteritis as a cause of gastrointestinal tract bleeding and protein-losing **enteropathy.**Eren M, Uluğ N, Aydemir Y.Turk Pediatri Ars. 2020 Sep 23;55(3):299-303. doi: 10.14744/TurkPediatriArs.2018.48376. eCollection 2020.PMID: 33061759

A Case of Eosinophilic Gastroenteritis Forming a Rigid Chamber Mimicking Giant Duodenal Ulcer on Computed Tomography Imaging. Am J Case Rep
. 2016 Apr 18;17:259-63

Eosinophilic ascites: an unusual manifestation of eosinophilic gastroenteritis. Int J Colorectal Dis
. 2020 Apr;35(4):765-767

Gastric outlet obstruction as manifestation of **eosinophilic gastroenteritis**. Rev Gastroenterol Peru. 2020 Apr-Jun;40(2):173-176.

There is no characteristic clinical picture of EC. It can be associated with abdominal pain, changes in bowel movements, diarrhoea and rectal bleeding. BMJ Case Rep. 2020 Sep 21;13(9):

Abdominal Pain Relieved By A Warm Hot Water Bottle: An Atypical Presentation Of Eosinophilic Gastroenteritis. Eur J Case Rep Intern Med
. 2020 May 12;7(8):

Retrospective cohort study at the University of North Carolina at Chapel Hill.

- Pathology reports of all patients who had undergone upper endoscopy with biopsy between 2000 and 2013 were obtained
- Cases of Eosinophilic gastroenteritis were defined
  - ≥20 eosinophils/hpf on either gastric **or** duodenal biopsy
  - symptoms attributable to the GI tract (i.e. abdominal pain, nausea, vomiting, weight loss, feeding intolerance, etc.)
  - no known secondary cause of eosinophilia.

Dig Liver Dis. 2015 Mar; 47(3): 197–201.

Symptoms, *N* (%)	
Dysphagia	12 (27)
Heartburn	8 (18)
Abdominal pain	28 (62)
Nausea	17 (38)
Vomiting	32 (71)
Chest pain	3 (7)
Bloating	8 (18)
	14 (31)
	15 (33)
Co	
	19 (42)
	12 (27)
	17 (38)
	14 (31)
	1 (16)
	29 (64)
	4 (9)
	14 (31)
Ascites	1 (2)
Small bowel obstruction	1 (2)
Food impaction	5 (11)
Weight loss >4 pounds	12 (27)
Protein losing enteropathy	3 (7)
Steatorrhea	1 (2)

Every patient has different manifestations – clinical assessment depends on presenting issues

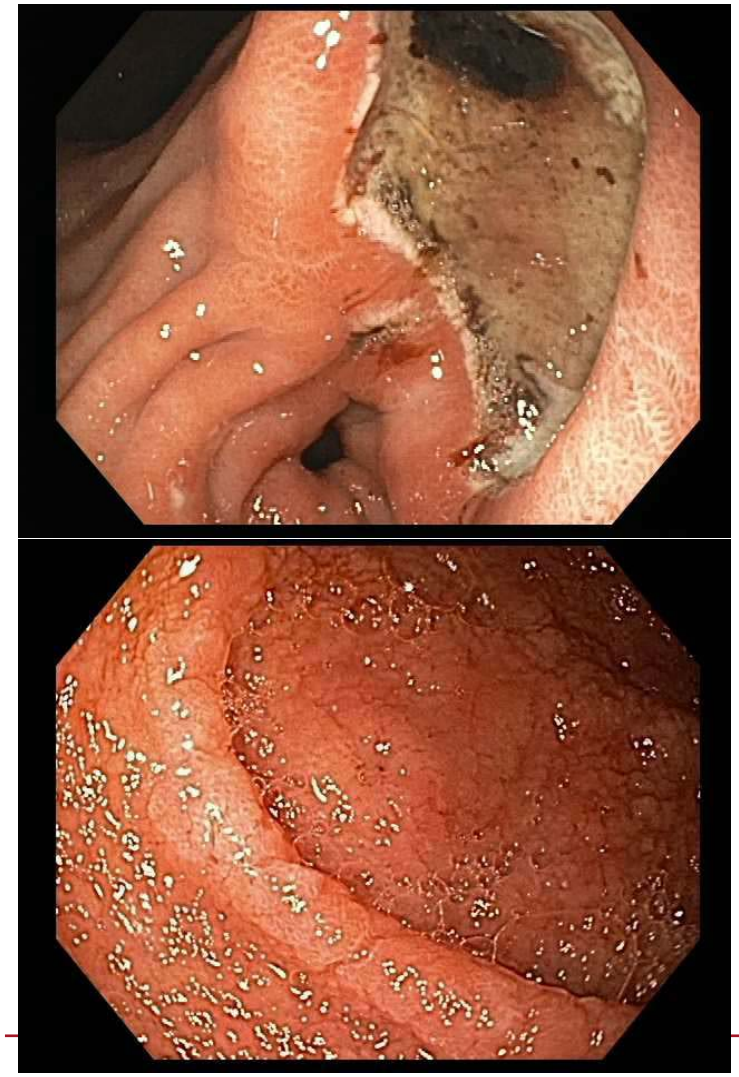
Cases underwent a mean of five endoscopic procedures per year.

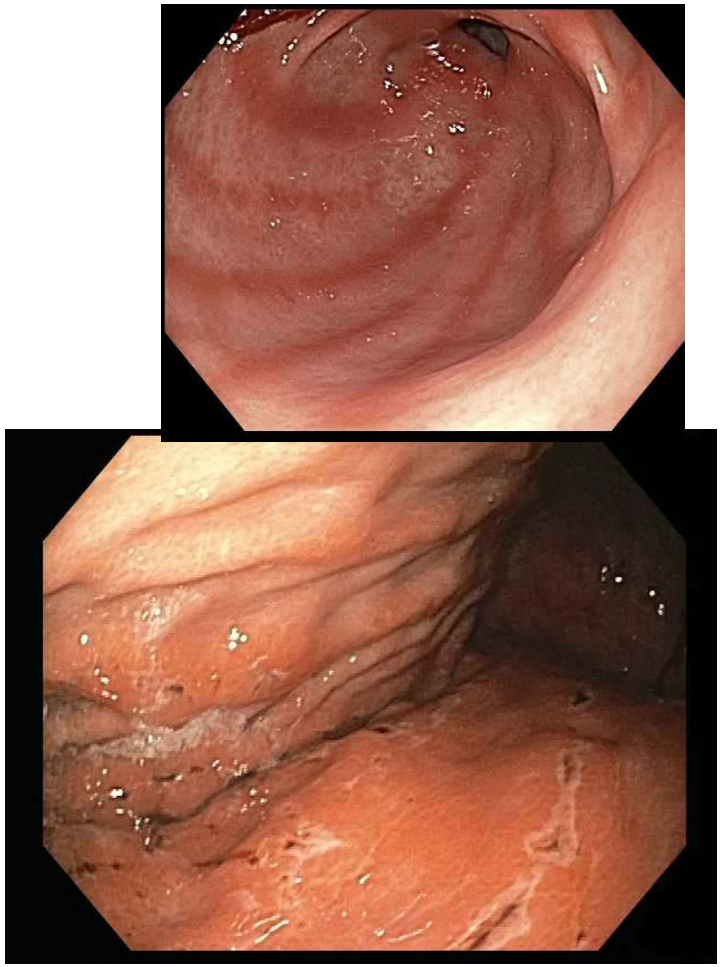
Variability of clinical manifestations

- **Symptom Scores**
  - Early Satiety
  - Bloating
  - Abdominal Pain
  - Abdominal Cramping
  - Loss of Appetite
  - Nausea
  - Diarrhea
  - Vomiting

N N Engl J Med. 2020 Oct 22;383(17):1624-1634, World J Gastroenterol 2017 May 21; 23(19): 3556-3564

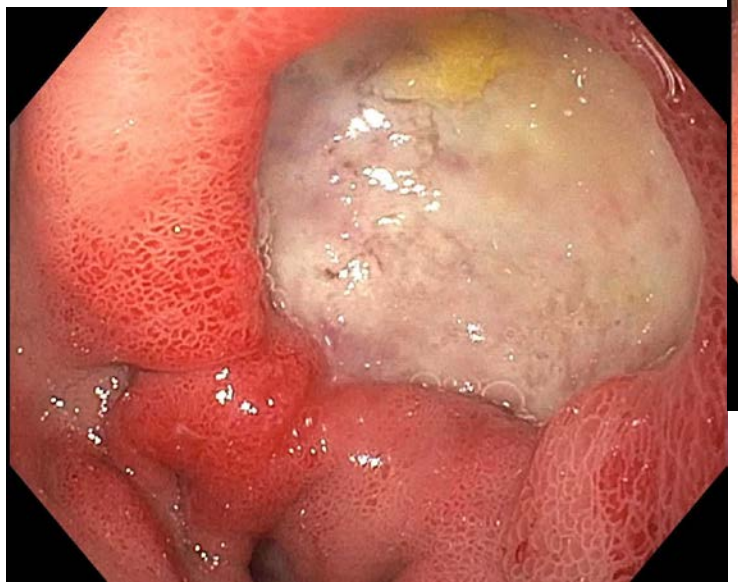
ENDOSCOPY - variability

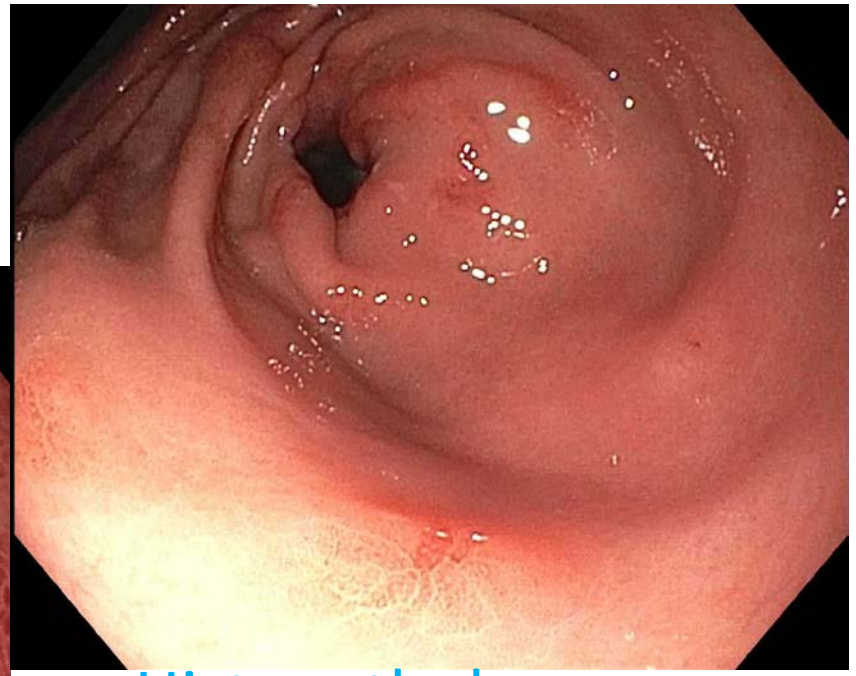




Endoscopy can mimic other disease

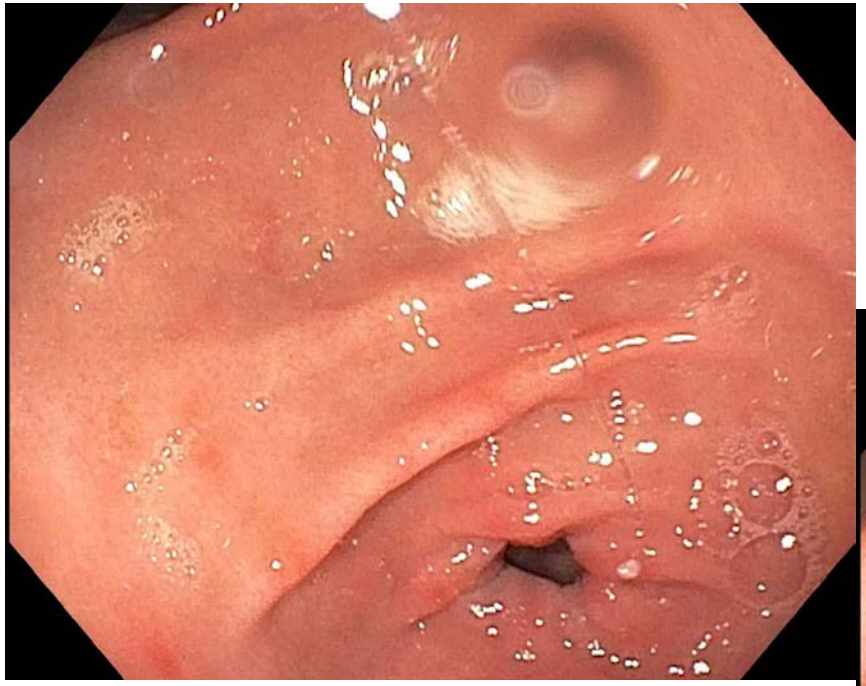
"UNREMARKABLE biopsies"



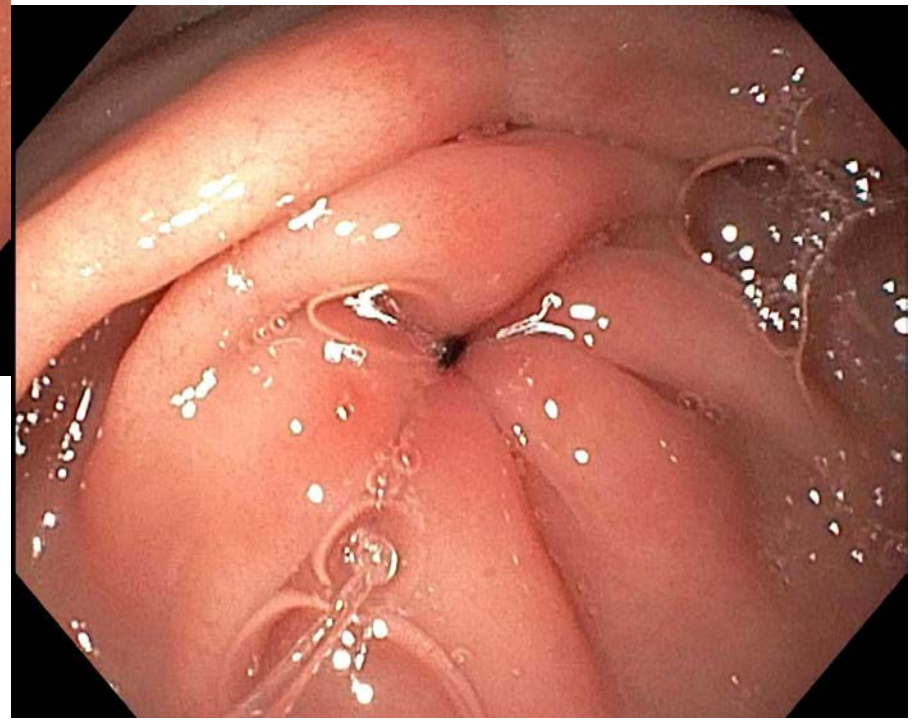


Histopathology variability/patchiness

FOLLOW UP



GASTRIC ANTRAL MUCOSA WITH NON-SPECIFIC REACTIVE CHANGES AND PROMINENT LAMINA PROPRIA EOSINOPHILS



Concerns with depending upon endoscopy/histopathology for diagnosis: outcomes

- Patchy involvement
  - Location of disease
- Up to 1/5 with normal endoscopies
- GI eosinophilia was patchy
  - average of only 2.6/8 gastric biopsies and 2.2/4 duodenal biopsies per subject met thresholds for EG/EoD.
  - Need multiple biopsies to identify disease

Clin Gastroenterol Hepatol . 2021 Jun 2;S1542-3565; Curr Gastroenterol Reports 2018; 20:37

Quality of life

- Psychological impact
- Impact on Social Relationships
- Financial Impact
- Impact on the Body

Digestive Diseases and Sciences (2018) 63:1148–1157

Before I was diagnosed, if I didn't believe in God I would
have committed suicide because of the pain. Because I
couldn't eat anything, it caused me great pain

I secluded myself at first because so much social dynamic is
around food and I just couldn't—it was hard for me to say
no. And then I still—a lot of friends didn't understand, I've
lost friends because they just didn't understand, because I
didn't understand

It can be tough sometimes to be on a strict diet and balance
the urge to eat food that I know I'm not supposed to eat due
to the allergies with the better feeling mentally and physically
that I get from not eating it"

I think last year we paid like 10 or 12 thousand dollars in
medical stuff… So the doctors' visits, and the tests, those
are super expensive

From a diagnosis point to going back to work, it was almost
a 3 year period for me to get through the depression and anxiety.

So I'm just sort of wondering what is my, realistically,
what is my life expectancy?"

Digestive Diseases and Sciences (2018) 63:1148–1157

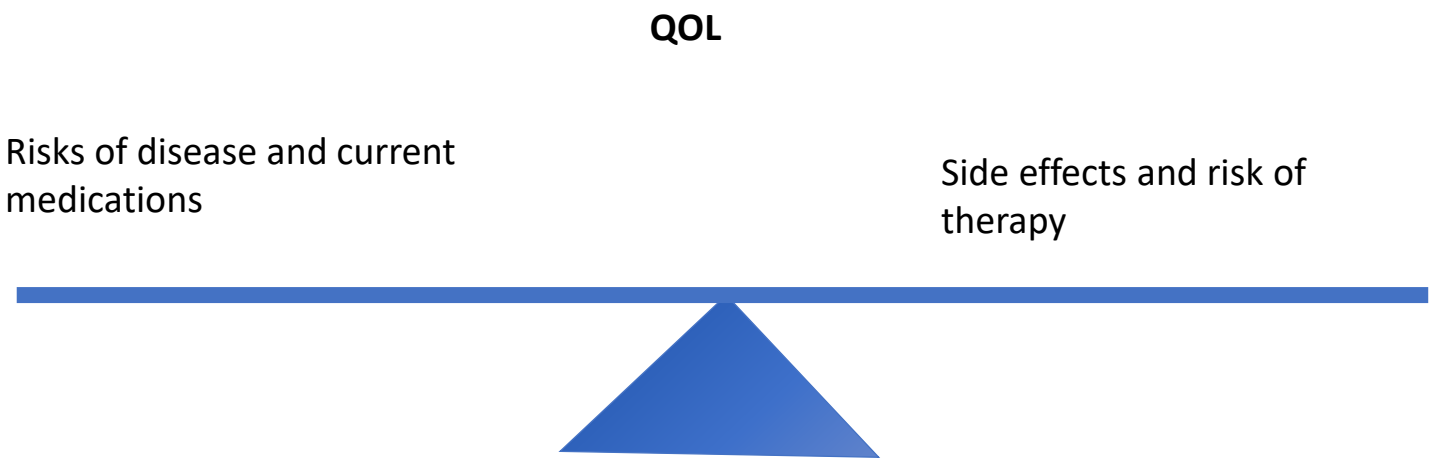
Summary:
Meaningful to the clinician-patient relationship

- **Quality of life**
  - Physical
  - Mental
  - Financial
- Endoscopy –
  - Most important for high risk
- Histopathology
  - Correlates with physical improvement?

Clinical improvement depends on presentation

- Can we control nausea?
  - Medications with cardiac side effects
  - Long term nausea from fibrosis
  - Motility d/o
- Can we improve malnutrition?
- Can we reverse iron deficiency?
- Can we give back a quality of life?

It is a balancing act



FDA GREAT IV on EGIDS, 7/21/2021

Clinician perspective on the assessment of meaningful benefit in pediatric patients

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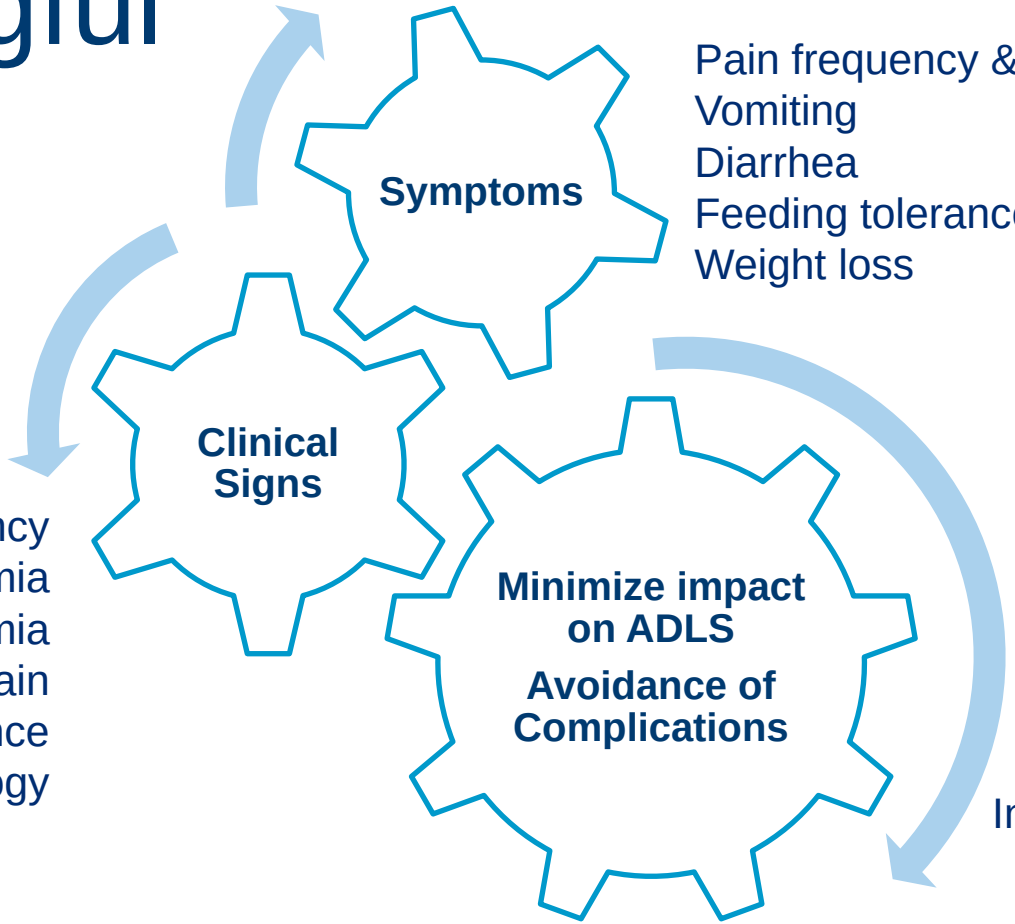
Department of Pediatrics
University of Colorado School of Medicine
Digestive Health Institute
Children's Hospital Colorado

Children's Hospital Colorado
Here, it's different.™

Disclosures

- No disclosures
- Will mention off label medication use.

Meaningful Benefit



Pain frequency & severity
Vomiting
Diarrhea
Feeding tolerance
Weight loss

Iron deficiency
Anemia
Hypoalbuminemia
Poor weight gain
Endoscopic appearance
Histology

Attend School/ Work/ Social
Avoidance of:
Malnutrition
GI bleeding
Perforation
Intestinal surgery

SJ

6 yo female with past history of eczema and food allergy presents with acute onset of vomiting, diarrhea and abdominal cramping. Symptoms of N/V, diarrhea, abdominal cramping persist and she is seen for evaluation.

No NSAID use.

No infectious exposures.

SJ: 6 yo

Slowed weight gain.

Abdominal xray: Ileus, no obstruction.

Laboratory:

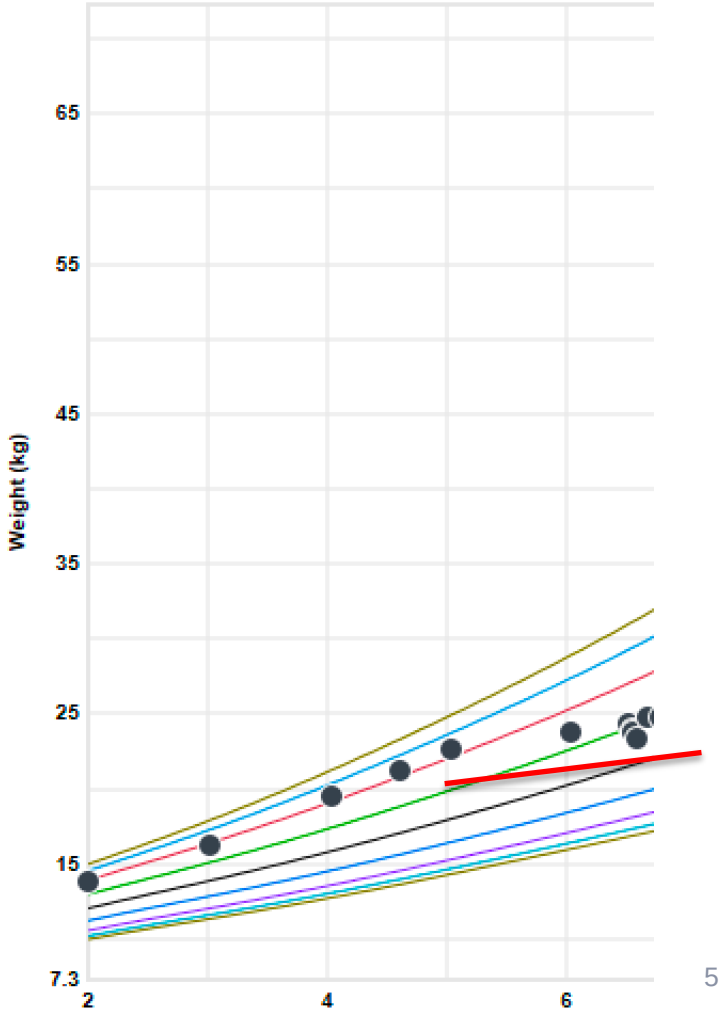
Normal albumin

Normal ferritin

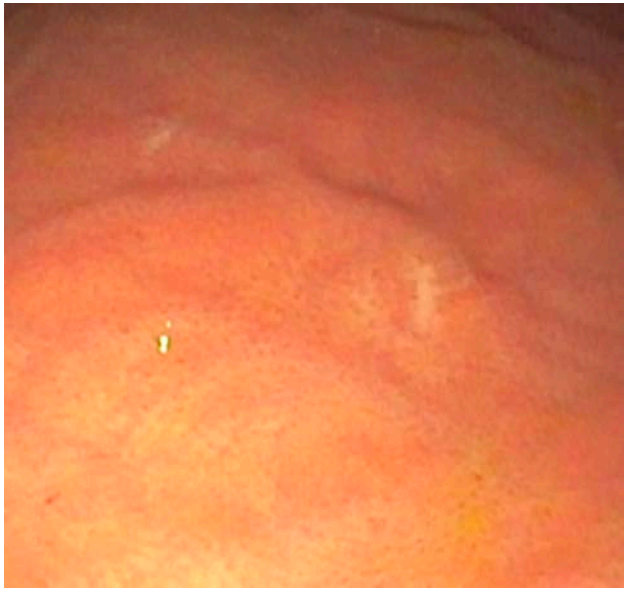
Unremarkable CBC. AEC 0.4 10^3/ul

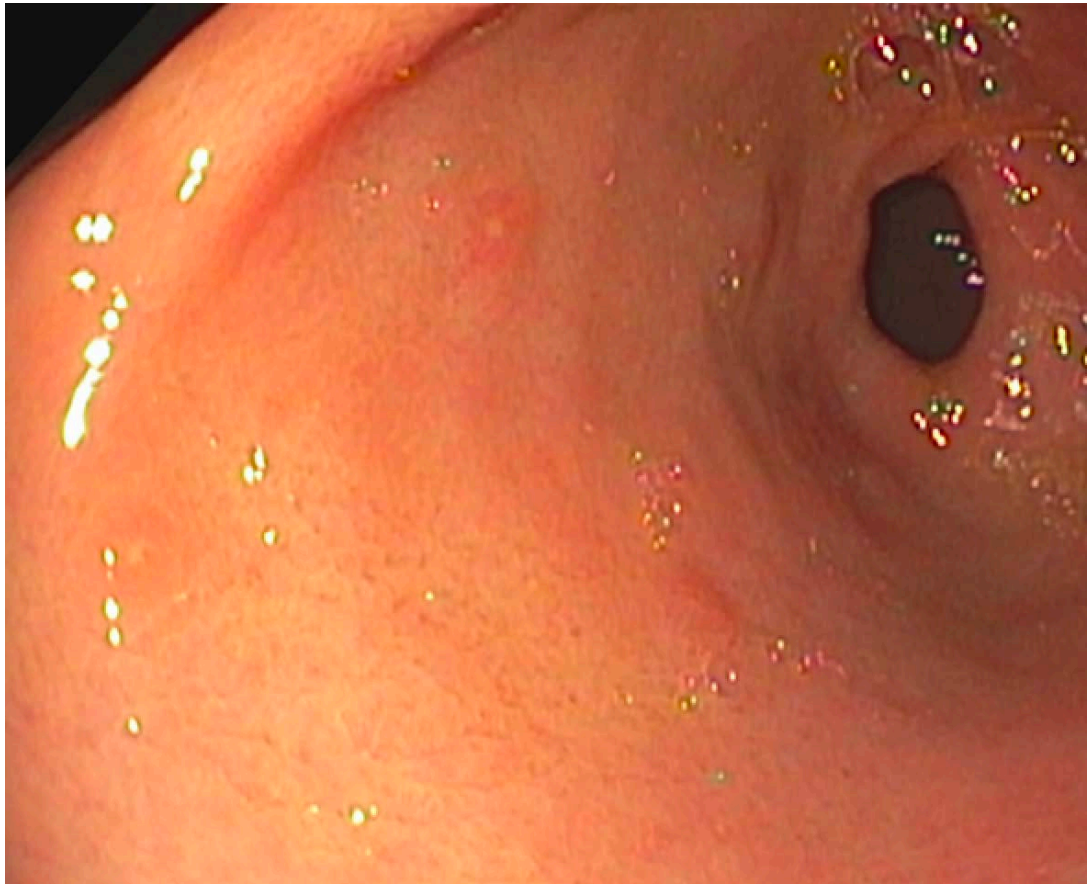
Normal celiac serology

Negative h pylori, crypto/giardia



SJ: Stomach





SJ: Histology

Stomach:

Reactive glandular architecture.

Lamina propria with up to 30 eos/hpf.

Epithelium is *eroded* above the largest cluster of eosinophils.

Degranulation is obvious with early lamina propria fibrosis.

No organisms seen.

Duodenum:

Blunted villous architecture.
Lamina propria with eosinophils, up to 100 eos/hpf.

Eosinophils are associated with *degranulation* and are focally within crypt epithelium.

SJ: Histology

Stomach:

Reactive glandular architecture.

Lamina propria with up to 30 eos/hpf.

Epithelium is *eroded* above the largest cluster of eosinophils.

Degranulation is obvious with early lamina propria fibrosis.

No organisms seen.

Duodenum:

Blunted villous architecture.
Lamina propria with eosinophils, up to 100 eos/hpf.

Eosinophils are associated with *degranulation* and are focally

Endoscopic appearance together with eosinophil activity provides convincing evidence of diagnosis.

SJ: follow up

Somewhat improved symptoms but still with intermittent abdominal pain and loose stools/diarrhea.

SJ: follow up

Somewhat improved symptoms but still with intermittent abdominal pain and loose stools/diarrhea.

EGD & Colonoscopy: again small aphthous ulcers in stomach. Normal colonoscopy.

Histology: Stomach with up to 112 eos/hpf with *degranulation and crypt invasion*.

SJ: Follow up

On this medication parents report Sydney has had *dramatic* improvement in pain and overall well being.

- Pain has largely resolved.
- Diarrhea has completely resolved.

Her appetite is excellent.

She has increased energy and has become more active again in activities - she is playing ice hockey.

Cortisol normal.

SJ: Follow up

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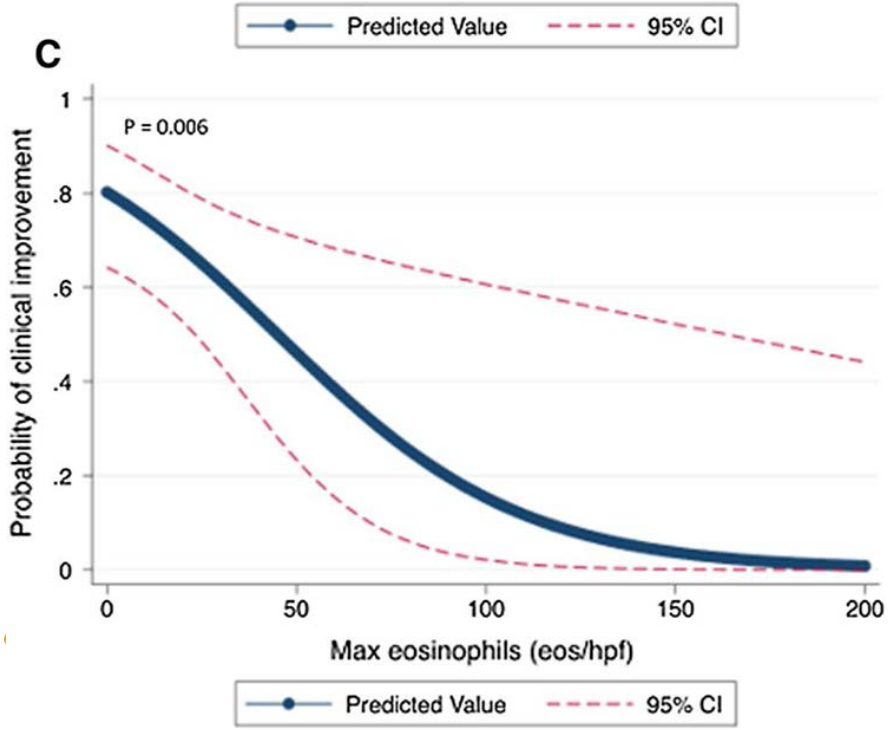
Perform EGD?

- No other clinical signs to assess.
- EGD/histology can demonstrate treatment effect and assist in next step treatment decisions.
- However symptom improvement, may be a more reliable assessment of endoscopic and histologic improvement than in EoE.

Ozdogan E.et al. AJG. 2021
Pesek R. et al. DDS. 2020

Symptom improvement may correlate with histology



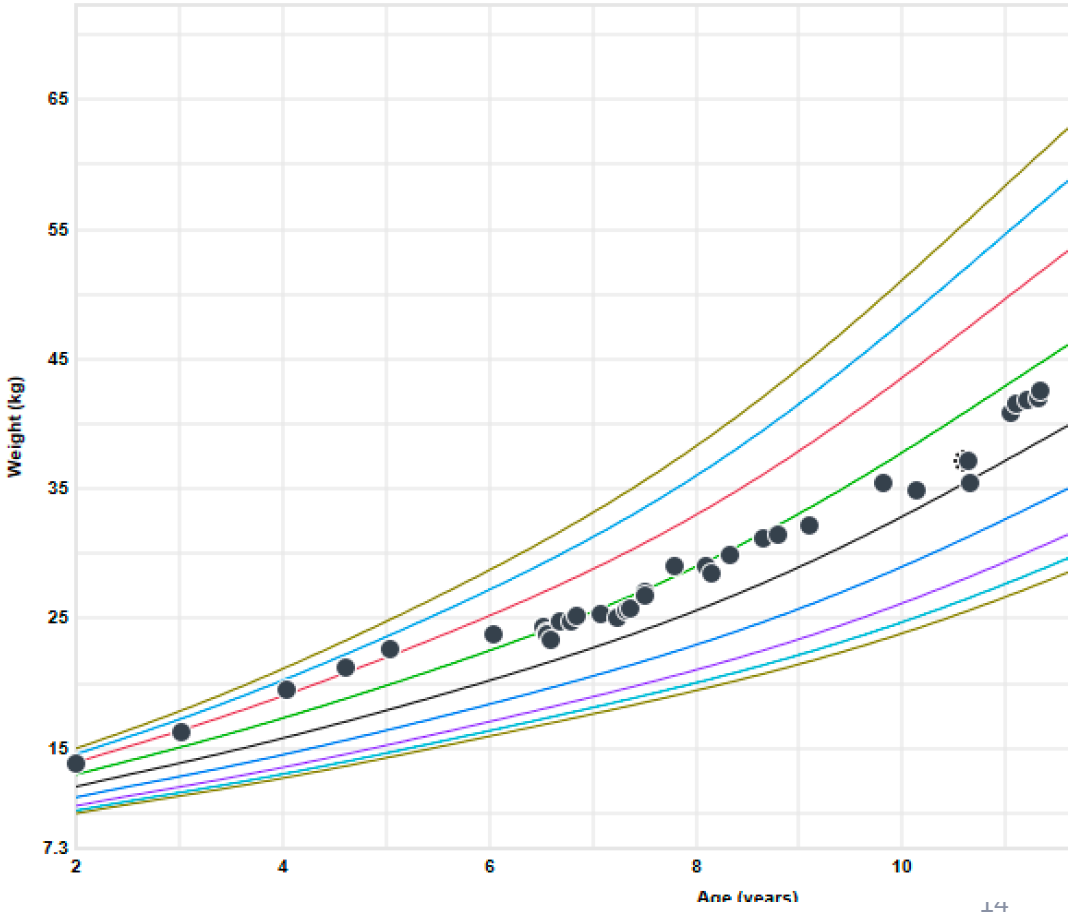
- 78% of patients with clinical improvement also had endoscopic improvement vs 55% in those without clinical improvement (p = 0.03).
- Post-treatment gastric eosinophil counts were significantly associated with clinical and endoscopic responses (p = 0.006 and p = 0.002, respectively).

Pesek R. et al. DDS. 2020

SJ: Follow up

Able to taper and then stop budesonide.

No flares for 2 years.



AD

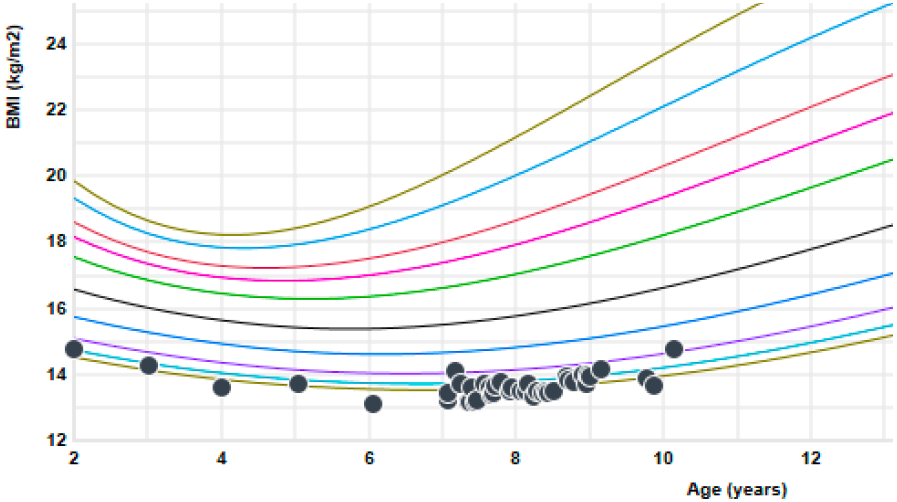
7 yo male presents to his pediatrician with severe fatigue, headaches and mild abdominal pain. Identified to have severe iron deficiency anemia.

Hemoglobin 4.4 g/dL

Ferritin <0.3 ng/mL

Unremarkable hematology evaluation.

Referred to GI.



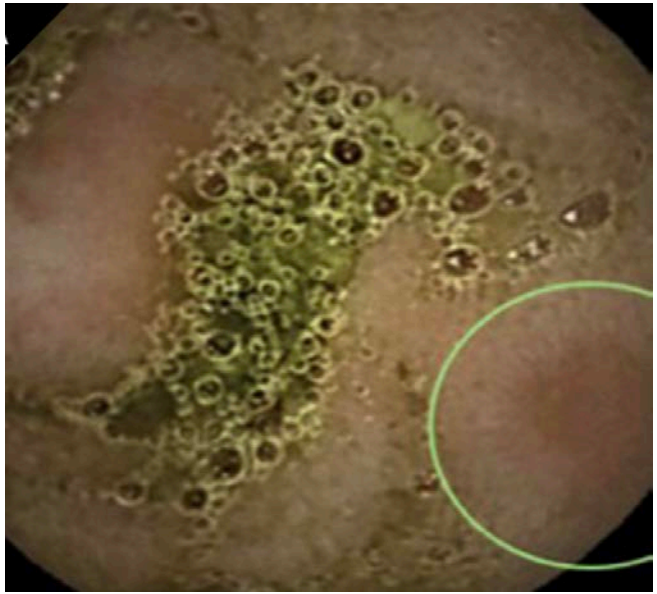
AD

Upper endoscopy:

Nodularity and erythema of the stomach with old blood. No ulcers or active bleeding

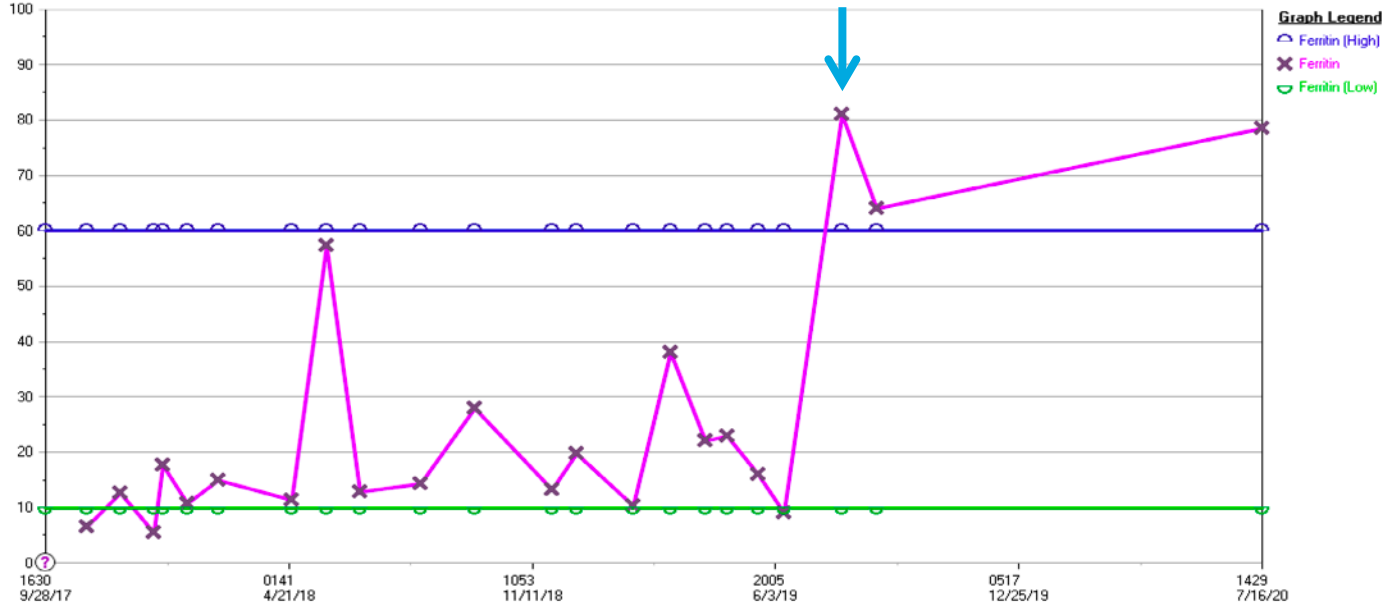
Capsule endoscopy:

Histology: Stomach with diffusely prominent eosinophils.



AD

Family has strong preferences to attempt dietary therapy, avoid all steroids and *minimize anesthesia*.



DW

17 yo presents with abdominal pain & nausea after being lost to follow up 6 years earlier.

At 11 yo, presented with abdominal pain and weight loss.

EGD: Erythema of duodenal bulb.

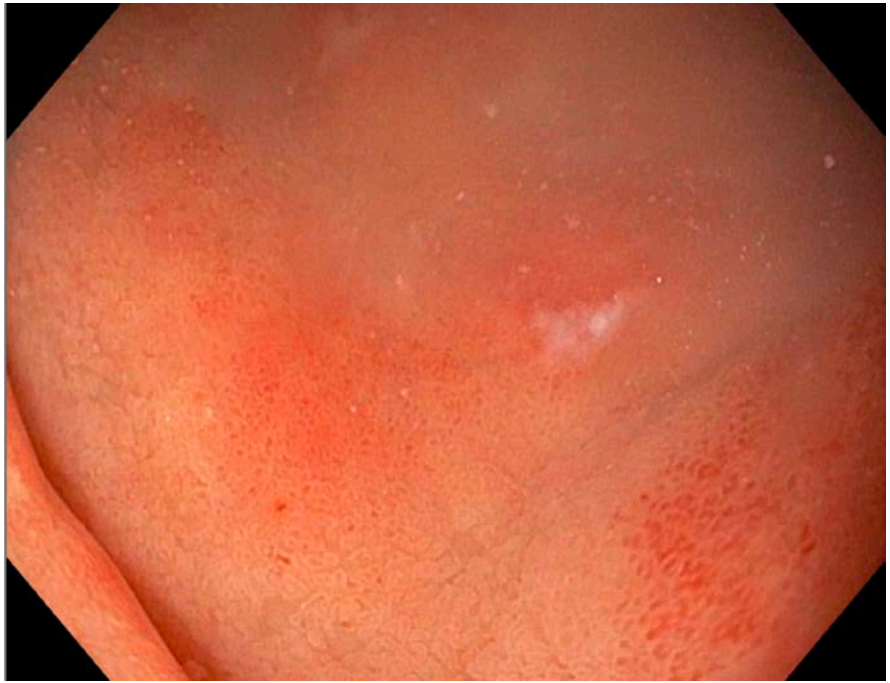
Histology: Eosinophilic inflammation of esophagus, stomach, duodenum. (>60 eos/hpf)

Normal UGI.

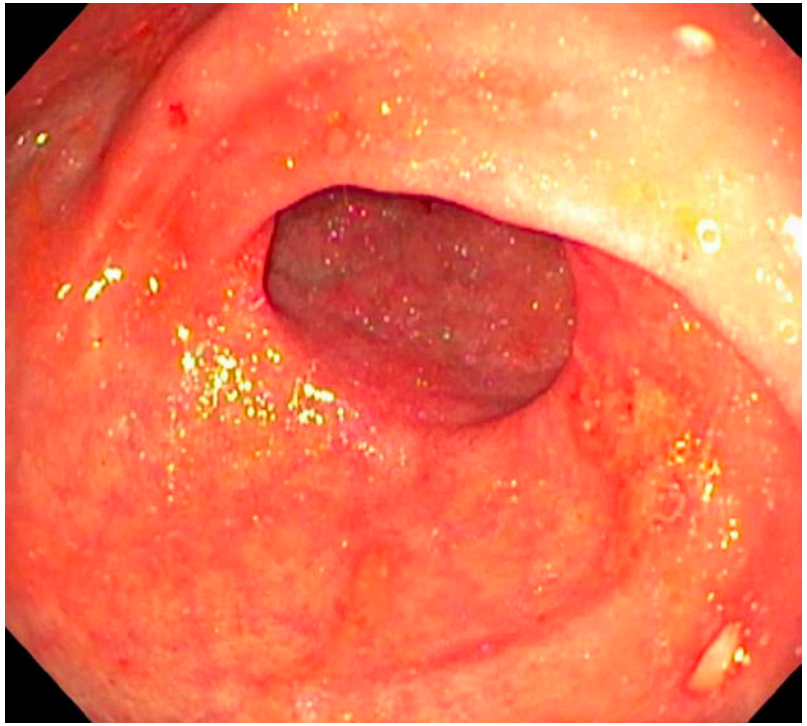
Treated with PPI but lost to follow up.

Symptoms had resolved until recently.

Now presents with symptoms of progressive daily epigastric abdominal pain with associated nausea but no vomiting.



DW

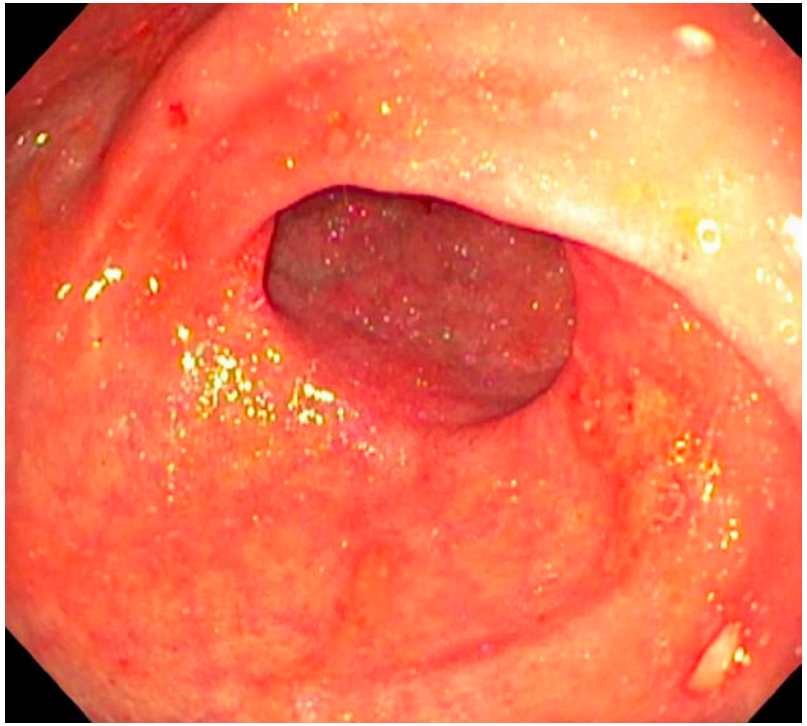


Duodenum: Active chronic duodenitis with villous blunting, mucin depletion and foveolar metaplasia. Mucosal eosinophilia (up to 60/hpf)

Stomach: Normal.

Esophagus, Distal: Mucosal eosinophils (up to 70/hpf) and reactive epithelial changes

DW



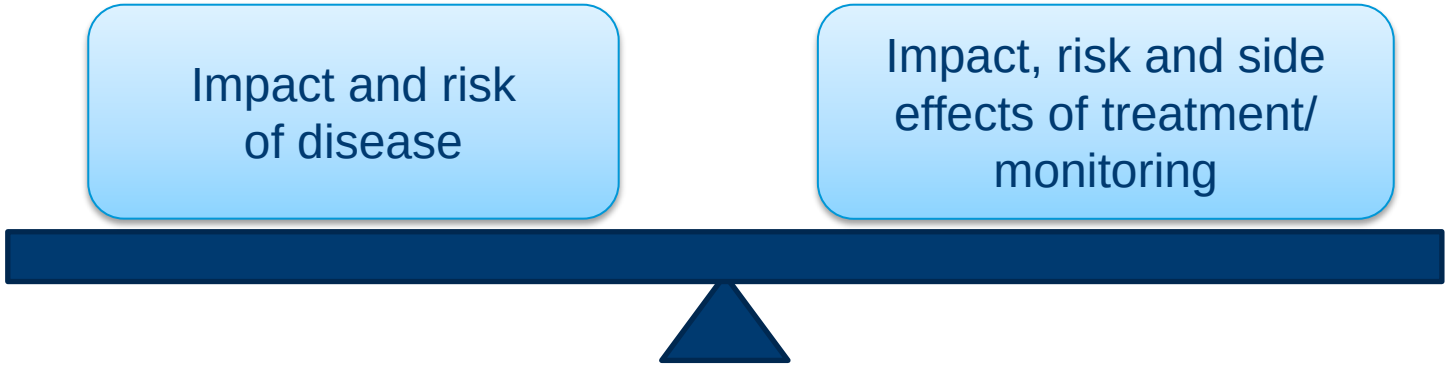
DW

Attempts with endoscopic dilation and treatment with corticosteroids.

Laparoscopic gastrojejunostomy.

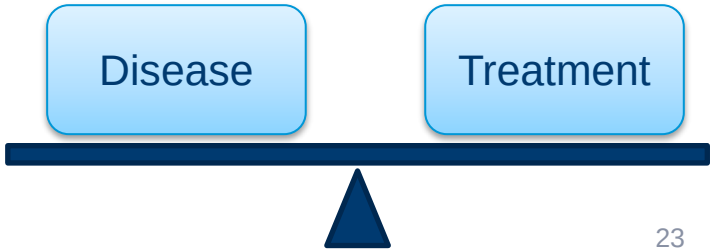
Summary of Assessment

- Upper endoscopy and/or histology
- Ferritin and/or albumin.
- Symptoms as described by patient/family.
- Capsule endoscopy or radiographic imaging.



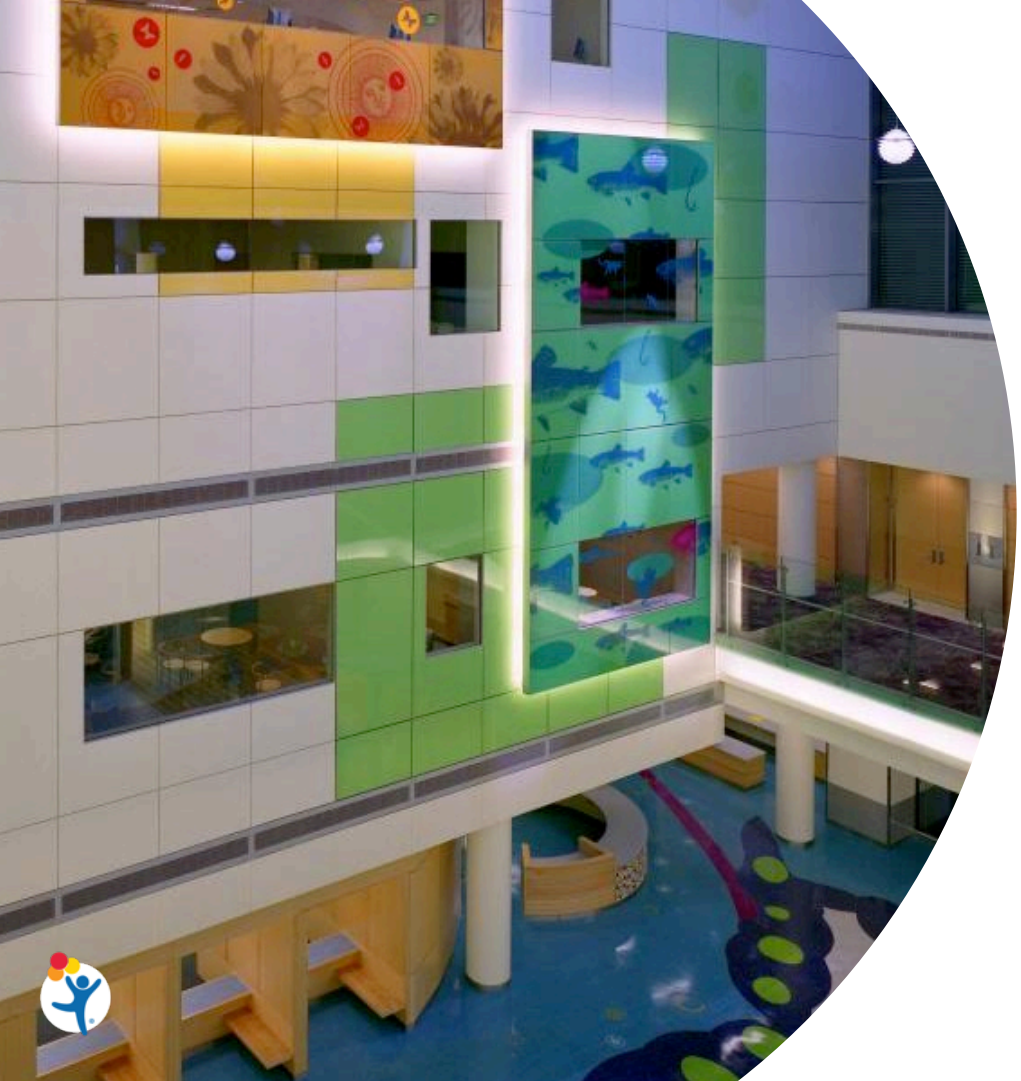
Timing of Assessments

- When attempting to adjust treatment.
- When treatment and symptom changes don’t align.
- Symptom assessment and laboratory monitoring between endoscopy/histology.



Summary of Assessment

- Endoscopic assessment with histology is helpful at providing objective information if treatment is impacting underlying pathology.
  - Is not without risks or cost.
  - Improvement in symptoms may correlate with reductions in tissue eosinophilia and endoscopic improvement.
- Non invasive assessments may be helpful in providing reassurance (or not) when attempting to minimize invasive testing.



BREAK – 15 MINUTES

PANEL DISCUSSION AND Q&A

PUBLIC WORKSHOP

U.S. FOOD & DRUG ADMINISTRATION

Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI):

Workshop on Eosinophilic Gastrointestinal Disorders Beyond EoE

July 21, 2021

Division of Gastroenterology (DG)
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research, FDA