Upper GI Potpourri: Celiac, Eosinophilic esophagitis, GERD

The Most Important Papers of the Last 12 Months

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Background

- To quote Bob Dylan, “the times they are a-changing’”
- Forces at play:
  - Rapidly advancing technology
  - New frontiers in basic science
  - Easier communication options
  - Expansion of publication venues
- Since last year alone on a pubmed search:
  - Esophagus: 7138
  - GERD: 1515
  - Celiac: 905
  - Eosinophilic esophagitis: 280

Topics to cover

- Reviewed the following journals:
  - American Journal of Gastroenterology
  - Clinical & Translational Gastroenterology
  - Clinical Gastroenterology & Hepatology
  - Diseases of the Esophagus
  - Gastroenterology
  - Gut
  - Lancet
  - Nature
  - Neurogastroenterology & Motility
  - New England Journal of Medicine
  - Science

Papers to discuss

1) AspECT study (Lancet 8/2018)
2) Lyon Consensus (Gut 7/2018)
3) AGREE Consensus (Gastroenterology 10/2018)
4) Natural Course of EoE (AJG 6/2018)
5) 4 Seminal papers on new technology
6) 3 Seminal papers on the esophageal microbiome
7) 3 Key abstracts & a key paper on celiac disease

AspECT Study

Articles

Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial

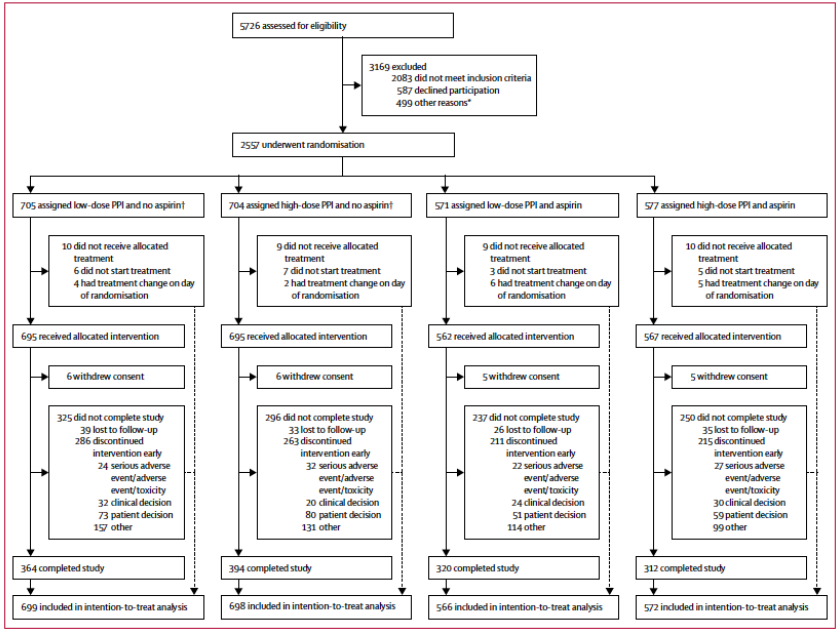
Janusz A Z Jankowski, John de Caestecker, Sharon B Love, Gavin Reilly, Peter Watson, Scott Sanders, Yeng Ang, Danielle Morris, Pradeep Bhandari, Claire Brooks, Stephen Attwood, Rebecca Harrison, Hugh Barr, Paul Moayyedi, the AspECT Trial Team*

Lancet 2018

AspECT Study

- Background: PPI & aspirin use have been suggested to potentially decrease cancer from Barrett's esophagus but data were limited
- Objective: To perform a large randomized study and definitively answer the question
- Study:
  - Randomized controlled trial of PPI/aspirin
    - High-dose PPI (esomeprazole 40 BID) vs. standard dose PPI (esomeprazole 20 daily)
    - Aspirin (300 mg or 325 mg) daily vs. no aspirin
  - 84 centers in the UK, 1 center in Canada
  - 2005-2017; 20,095 patient years & median follow-up 8.9 years

AspECT Study



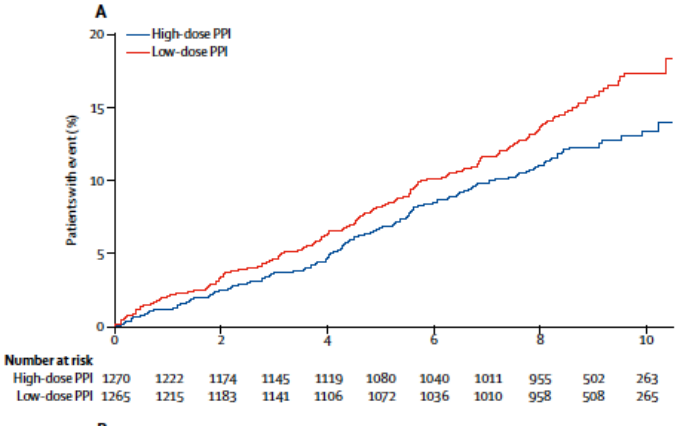
AspECT Study

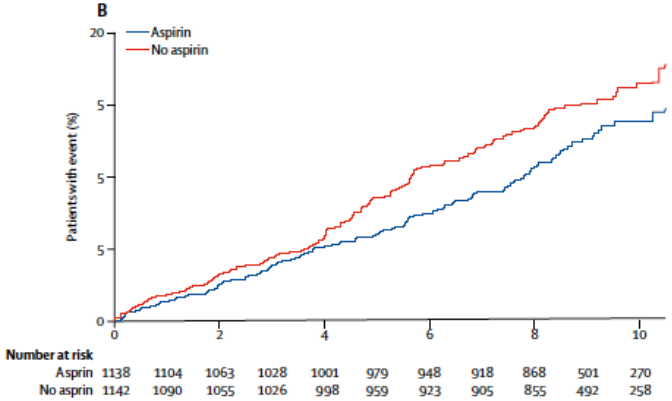
	Low-dose PPI (n=1265)	High-dose PPI (n=1270)	No aspirin (n=1142)	Aspirin (n=1138)
Length of Barrett's metaplasia at randomisation (strata for minimisation, cm)*	4 (3–6)	4 (2–6)	4 (2–6)	4 (3–6)
Length of Barrett's oesophagus (stratification group, cm)				
<2	123 (10%)	124 (10%)	108 (9%)	109 (10%)
2–3	434 (34%)	435 (34%)	398 (35%)	395 (35%)
3–8	538 (43%)	539 (42%)	491 (43%)	493 (43%)
>8	130 (10%)	129 (10%)	117 (10%)	118 (10%)
Tongues	40 (3%)	43 (3%)	28 (2%)	23 (2%)
Age (strata for minimisation, years)	59 (51–65)	59 (51–65)	58 (50–64)	58 (50–65)
Age (stratification grouping, years)				
<50	283 (22%)	280 (22%)	269 (24%)	272 (24%)
50–60	388 (31%)	390 (31%)	365 (32%)	358 (31%)
60–70	447 (35%)	445 (35%)	386 (34%)	388 (34%)
>70	147 (12%)	155 (12%)	122 (11%)	122 (11%)
Intestinal metaplasia				
Yes	1130 (89%)	1136 (89%)	1042 (91%)	1035 (91%)
No	134 (11%)	134 (11%)	100 (9%)	103 (9%)
Sex				
Male	1012 (80%)	1010 (80%)	900 (79%)	896 (79%)
Female	253 (20%)	260 (20%)	242 (21%)	242 (21%)

The length of Barrett's oesophagus stratification group was required for randomisation. The actual length of Barrett's oesophagus was collected on the baseline data form. PPI=proton-pump inhibitor (esomeprazole). *Data missing from 122 patients.

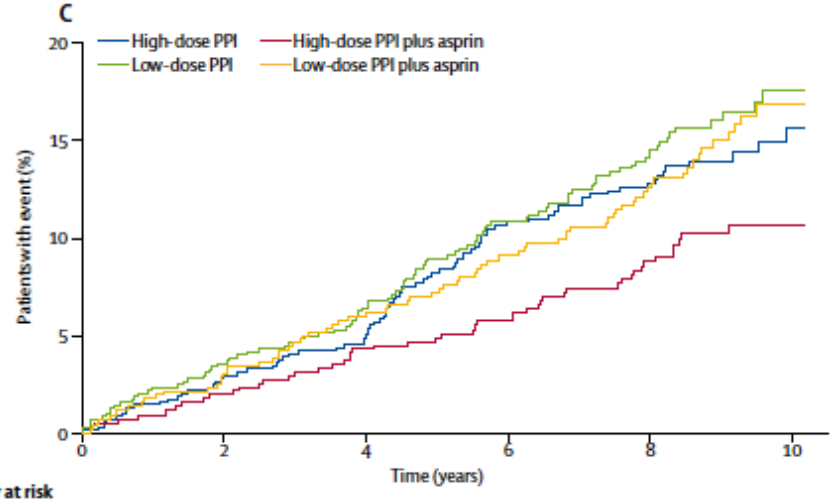
Table 1: **Baseline characteristics by treatment group**

AspECT Study





AspECT Study



Number at risk											
High-dose PPI	698	668	644	629	616	587	563	552	523	260	128
High-dose PPI plus aspirin	572	554	530	516	503	493	477	459	432	242	135
Low-dose PPI	699	665	650	629	608	586	565	551	522	249	130
Low-dose PPI plus aspirin	566	550	533	512	498	486	471	459	436	259	135

AspECT Study

	High-dose PPI vs low-dose PPI					Aspirin vs no aspirin				
	Total number of patients in analysis	Events/ patients on high-dose PPI	Events/ patients on low-dose PPI	Time ratio (95% CI)	p value	Total number of patients in analysis	Events/ patients on aspirin	Events/ patients not on aspirin	Time ratio (95% CI)	p value
All-cause mortality	2535	79/1270	105/1265	1·36 (1·01–1·82)	0·039	2280	73/1138	90/1142	1·25 (0·92–1·70)	0·16
Oesophageal adenocarcinoma	2535	40/1270	41/1265	1·04 (0·67–1·61)	0·86	2280	35/1138	35/1142	1·02 (0·64–1·64)	0·92
High-grade dysplasia	2535	44/1270	59/1265	1·36 (0·92–2·02)	0·12	2280	37/1138	55/1142	1·51 (1·00–2·29)	0·053
Cause-specific mortality	2535	8/1270	12/1265	1·55 (0·63–3·80)	0·34	2280	8/1138	8/1142	1·01 (0·38–2·69)	0·98
Composite endpoint, men only	2022	118/1010	148/1012	1·26 (0·99–1·61)	0·06	1796	105/896	130/900	1·26 (0·98–1·64)	0·07
Composite endpoint, women only	513	21/260	26/253	1·27 (0·72–2·27)	0·41	484	22/242	24/242	1·13 (0·63–2·02)	0·69

PPI=proton pump inhibitor (esomeprazole).

Table 2: **Accelerated failure time modelling for secondary endpoints**

AspECT Study

- Summary
  - High-dose PPI protects against a composite endpoint of all-cause mortality, high-grade dysplasia and esophageal cancer
  - Aspirin protected against the endpoint if patients taking another NSAID were excluded
  - Affects of PPI and aspirin seemed to be additive
- Limitations
  - Despite massive size, only statistical endpoint reached was all-cause mortality
  - Large number needed to treat:
    - High-dose vs. Low-dose PPI: NNT 34
    - Aspirin vs. no aspirin: NNT 43
  - Most patients had long-segment Barrett's esophagus (> 3 cm)
  - Side effects not insignificant

Lyon Consensus

Modern diagnosis of GERD: the Lyon Consensus

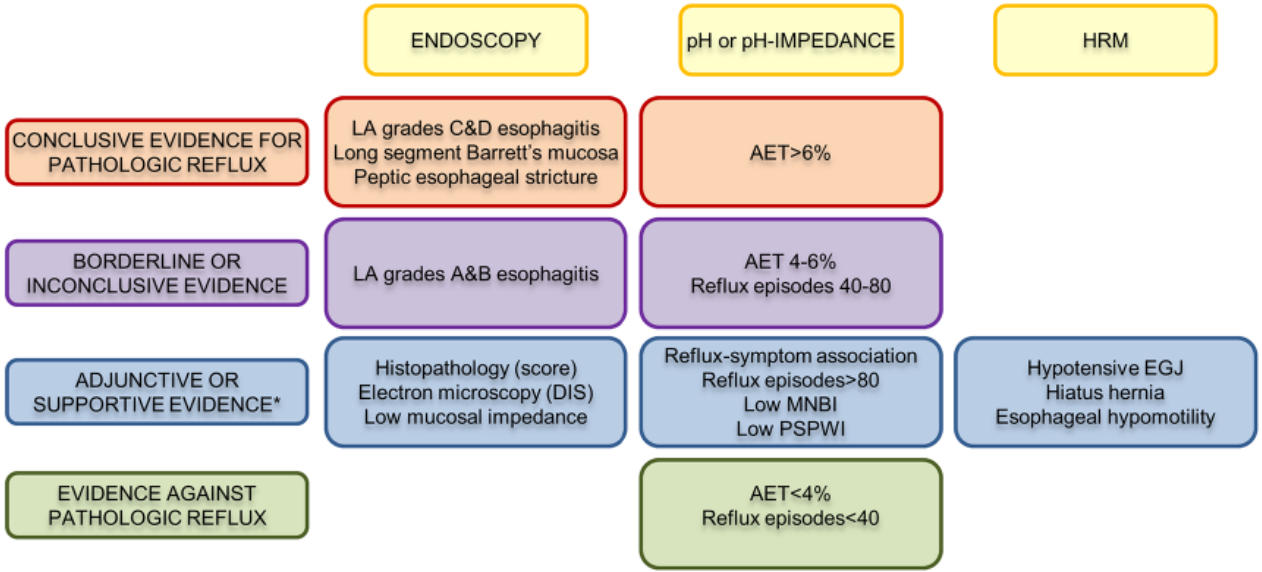
C Prakash Gyawali,[1] Peter J Kahrilas,[2] Edoardo Savarino,[3] Frank Zerbib,[4] Francois Mion,[5,6,7] André J P M Smout,[8] Michael Vaezi,[9] Daniel Sifrim,[10] Mark R Fox,[11,12] Marcelo F Vela,[13] Radu Tutuian,[14] Jan Tack,[15] Albert J Bredenoord,[8] John Pandolfino,[2] Sabine Roman[5,6,7]

Gut 2018

Lyon Consensus

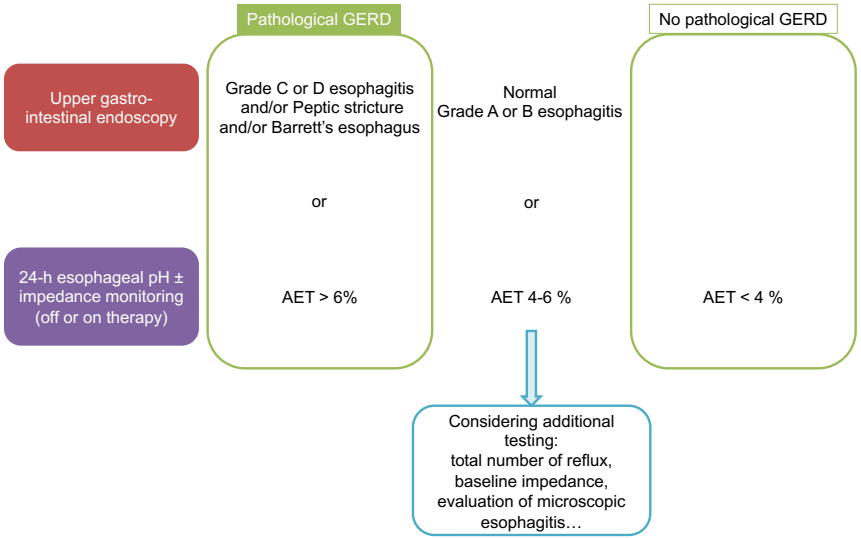
- Background:
  - Prior criteria for GERD were often binary
  - New technology has raised as many questions and answers
  - Need to standardize

Lyon Consensus



Lyon Consensus

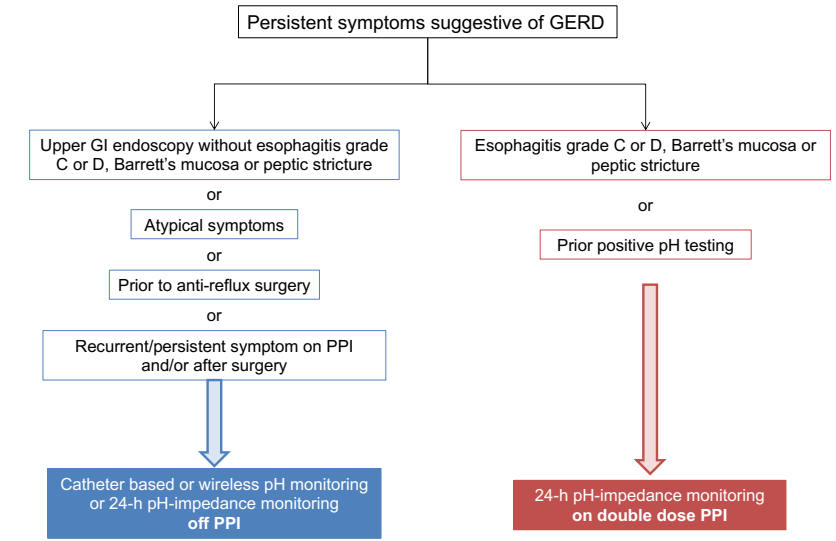
Figure 2



Slide courtesy of Prakash Gyawali

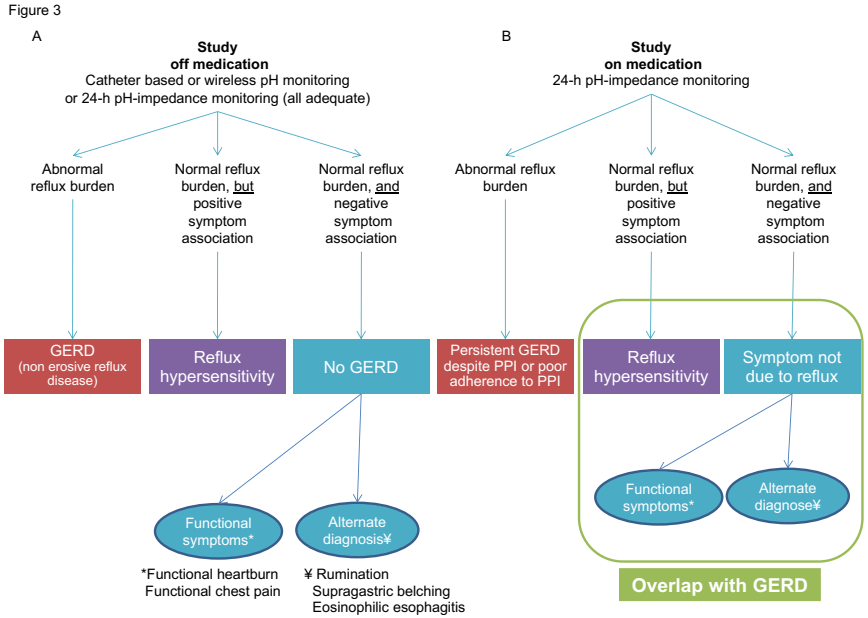
Lyon Consensus

Figure 1



Slide courtesy of Prakash Gyawali

Lyon Consensus



Slide courtesy of Prakash Gyawali

AGREE Consensus

Gastroenterology 2018;155:1022–1033

CLINICAL—ALIMENTARY TRACT

Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference

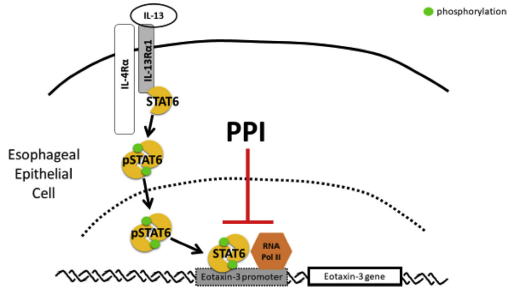
Evan S. Dellon,[1,*] **Chris A. Liacouras**,[2,*] **Javier Molina-Infante**,[3,*] **Glenn T. Furuta**,[4,*] Jonathan M. Spergel,[5] Noam Zevit,[6] Stuart J. Spechler,[7] Stephen E. Attwood,[8] Alex Straumann,[9] Seema S. Aceves,[10] Jeffrey A. Alexander,[11] Dan Atkins,[12] Nicoleta C. Arva,[13] Carine Blanchard,[14] Peter A. Bonis,[15] Wendy M. Book,[16] Kelley E. Capocelli,[17] Mirna Chehade,[18] Edaire Cheng,[19] Margaret H. Collins,[20] Carla M. Davis,[21] Jorge A. Dias,[22] Carlo Di Lorenzo,[23] Ranjan Dohil,[24] Christophe Dupont,[25] Gary W. Falk,[26] Cristina T. Ferreira,[27] Adam Fox,[28] Nirmala P. Gonsalves,[29] Sandeep K. Gupta,[30] David A. Katzka,[11] Yoshikazu Kinoshita,[31] Calies Menard-Katcher,[4] Ellyn Kodroff,[32] David C. Metz,[26] Stephan Miehlke,[33] Amanda B. Muir,[2] Vincent A. Mukkada,[34] Simon Murch,[35] Samuel Nurko,[36] Yoshikazu Ohtsuka,[37] Rok Orel,[38] Alexandra Papadopoulou,[39] Kathryn A. Peterson,[40] Hamish Philpott,[41] Philip E. Putnam,[34] Joel E. Richter,[42] Rachel Rosen,[43] Marc E. Rothenberg,[44] Alain Schoepfer,[45] Melissa M. Scott,[46] Neil Shah,[47] Javed Sheikh,[48] Rhonda F. Souza,[7] Mary J. Strobel,[16] Nicholas J. Talley,[49] Michael F. Vaezi,[50] Yvan Vandenplas,[51] Mario C. Vieira,[52] Marjorie M. Walker,[53] Joshua B. Wechsler,[54] Barry K. Wershil,[54] Ting Wen,[44] Guang-Yu Yang,[55] Ikuo Hirano,[29,§] and Albert J. Bredenoord[56,§]

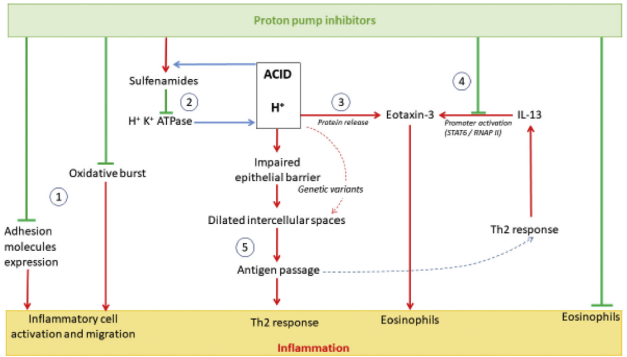
Gastroenterology 2018

AGREE Consensus

- Background:
  - Research has changed the field of EoE quickly
  - PPIs are now recognized as a treatment strategy for eosinophilia with mechanisms independent from ant-acid effects

AGREE Consensus





AGREE Consensus

- Take-home point:
  - EoE should be diagnosed when biopsies show at least 15 eos/hpf in the appropriate clinical situation
  - PPI use is no longer part of the diagnostic pathway
  - If patients improve with a PPI it does not imply reflux is the cause
  - PPI-responsive esophageal eosinophilia is no longer a diagnosis

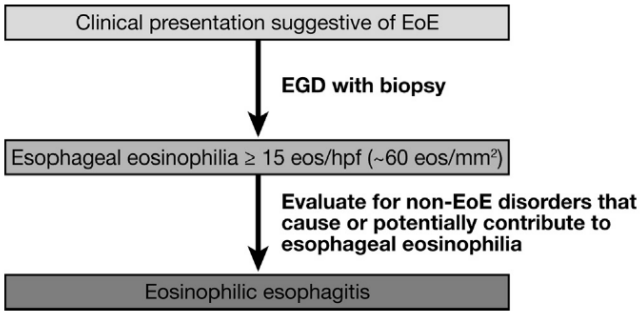


Figure 1. Updated EoE diagnostic algorithm.

Natural History of EoE

The Natural Course of Eosinophilic Esophagitis and Long-Term Consequences of Undiagnosed Disease in a Large Cohort

Marijn J. Warners, MD, PhD[1], Renske A. B. Oude Nijhuis, MD[1], Laetitia R. H. de Wijkerslooth, MD, PhD[2], Andreas J. P. M. Smout, MD, PhD[1] and Albert J. Bredenoord, MD, PhD[1]

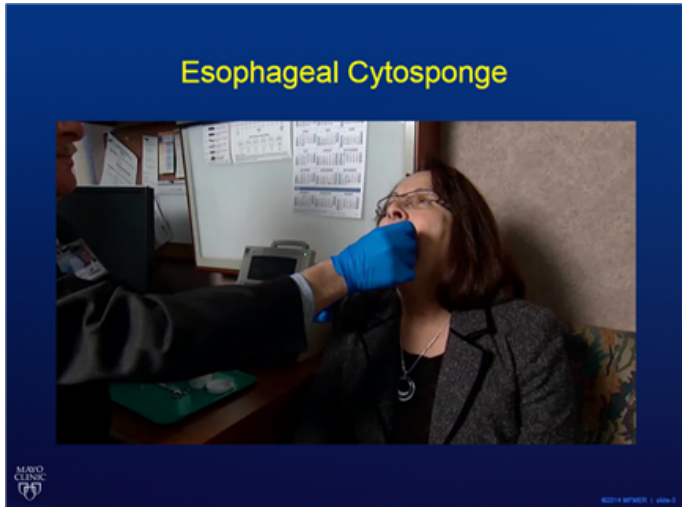
American Journal of Gastroenterology 2018

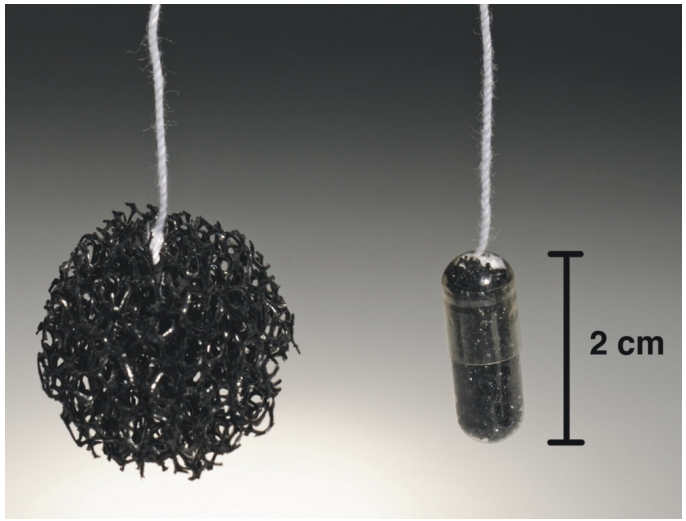
Natural History of EoE

- Retrospective study of 721 patients in the Netherlands from 1996 – 2015
- Fibrosis seen:
  - Adults: 76%
  - Children: 39%
- The longer between onset of symptoms and diagnosis, the higher the risk of strictures & food impaction (19% versus 57%)
- With each additional year of undiagnosed EoE the risk of stricture increases by 9%

Seminal Papers on New Technology

Cytosponge





Images courtesy of Dave Katzka

Cytosponge

Clinical Gastroenterology and Hepatology 2019;17:647–656

Safety and Acceptability of Esophageal Cytosponge Cell Collection Device in a Pooled Analysis of Data From Individual Patients

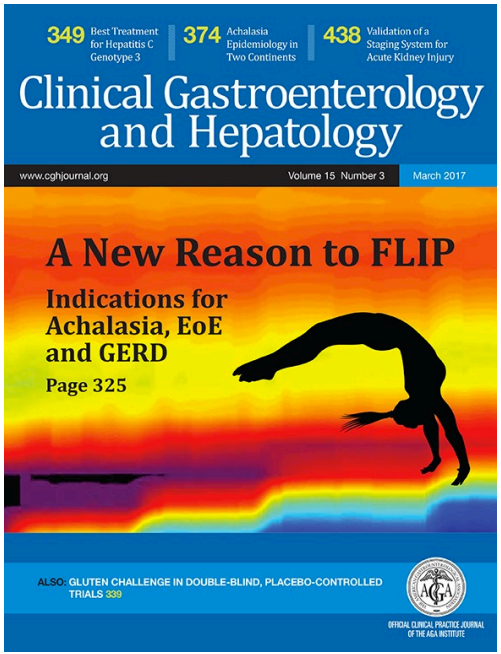
Wladyslaw Januszewicz,[*,‡,a] Wei Keith Tan,[*,§,a] Katie Lehovsky,[‖] Irene Debiram-Beecham,[*] Tara Nuckcheddy,[*] Susan Moist,[¶] Sudarshan Kadri,[#] Massimiliano di Pietro,[*] Alex Boussioutas,[**,‡‡] Nicholas J. Shaheen,[§§] David A. Katzka,[‖‖] Evan S. Dellon,[§§] and Rebecca C. Fitzgerald,[*] on behalf of the BEST1 and BEST2 study investigators

Highly Discriminant Methylated DNA Markers for the Non-endoscopic Detection of Barrett's Esophagus

Prasad G. Iyer, MD, MSc[1], William R. Taylor, MS[1], Michele L. Johnson, CCRP[1], Ramona L. Lansing, RN[1], Kristyn A. Maixner, APRN[1], Tracy C. Yab, MBA[1], Julie A. Simonson, CCRP[1], Mary E. Devens, RN[1], Seth W. Slettedahl, BS[2], Douglas W. Mahoney, MS[2], Calise K. Berger, BS[1], Patrick H. Foote, BS[1], Thomas C. Smyrk, MD[3], Kenneth K. Wang, MD[1], Herbert C. Wolfsen, MD[4] and David A. Ahlquist, MD[1]

Clinical Gastroenterology & Hepatology 2019
American Journal of Gastroenterology 2018

Functional Lumen Imaging Probe



Normal Values of Esophageal Distensibility and Distension-Induced Contractility Measured by Functional Luminal Imaging Probe Panometry

Dustin A. Carlson,* Wenjun Kou,* Zhiyue Lin,* Monique Hinchcliff,‡ Anjali Thakrar,‡ Sophia Falmagne,* Jacqueline Prescott,* Emily Dorian,* Peter J. Kahrilas,* and John E. Pandolfino*

Division of Gastroenterology and Hepatology, ‡Division of Rheumatology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Clinical Gastroenterology & Hepatology 2017
Clinical Gastroenterology & Hepatology 2019

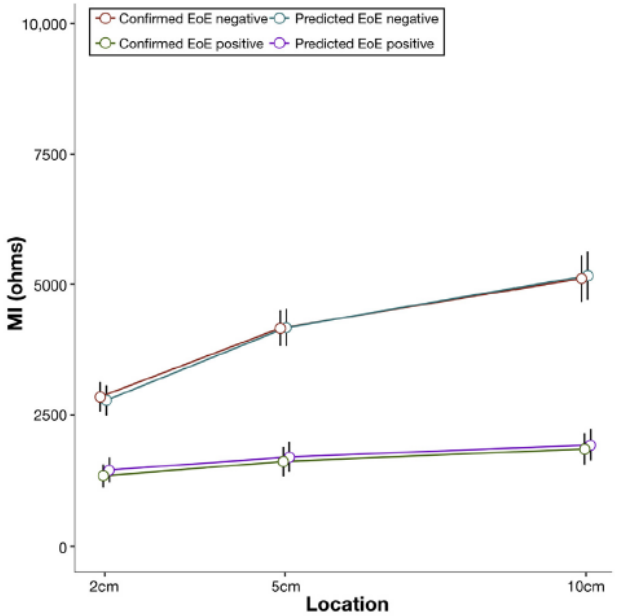
Mucosal Impedance

- Balloon with impedance sensors that can be placed during endoscopy in real time
- Previously shown to separate GERD from normal with good reliability

Deflated

Inflated

Mucosal Impedance



Clinical Gastroenterology and Hepatology 2018;16:664–671

ALIMENTARY TRACT

Esophageal Mucosal Impedance Patterns Discriminate Patients With Eosinophilic Esophagitis From Patients With GERD

Yash Choksi,* Pooja Lal,* James C. Slaughter,‡ Rohit Sharda,* Jacob Parnell,* Tina Higginbotham,* and Michael F. Vaezi*

*Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University School of Medicine, Nashville, Tennessee; ‡Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, Tennessee

Clinical Gastroenterology & Hepatology 2018

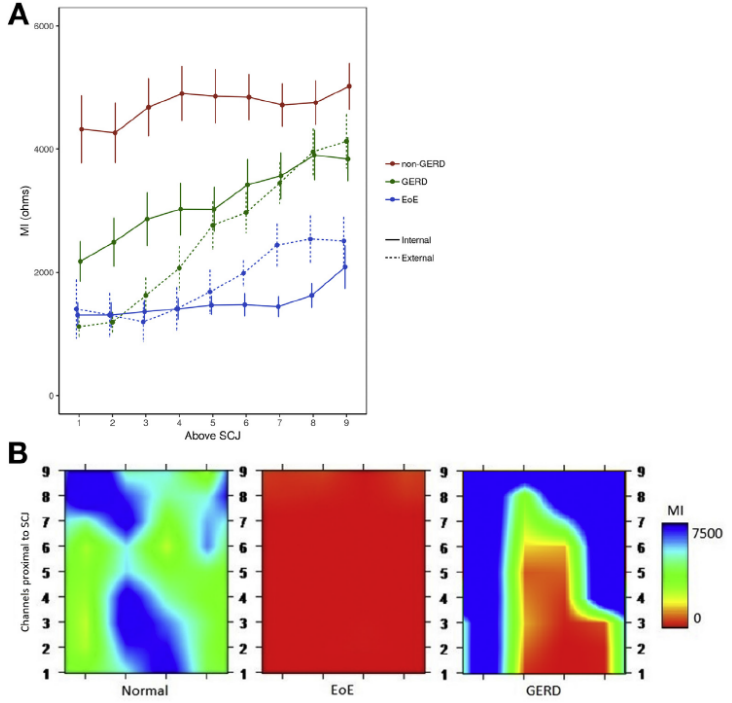
Gastroenterology 2019;156:1617–1626

CLINICAL—ALIMENTARY TRACT

Development and Validation of a Mucosal Impedance Contour Analysis System to Distinguish Esophageal Disorders

Dhyanesh A. Patel,[1] Tina Higginbotham,[1] James C. Slaughter,[2] Muhammad Aslam,[1] Elif Yuksel,[3] David Katzka,[4] C. Prakash Gyawali,[5] Melina Mashi,[6] John Pandolfino,[6] and Michael F. Vaezi[1]

[1]Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center, Nashville, Tennessee; [2]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee; [3]Department of Gastroenterology, Izmir Ataturk Teaching and Research Hospital, Katip Celebi University, Izmir, Turkey; [4]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [5]Division of Gastroenterology, Washington University Medical Center, St Louis, Missouri; and [6]Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois



Esophageal Microbiome

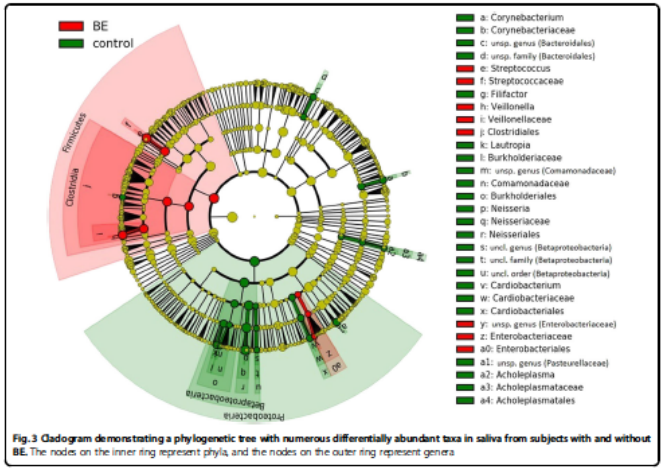


Fig. 3 Cladogram demonstrating a phylogenetic tree with numerous differentially abundant taxa in saliva from subjects with and without BE. The nodes on the inner ring represent phyla, and the nodes on the outer ring represent genera

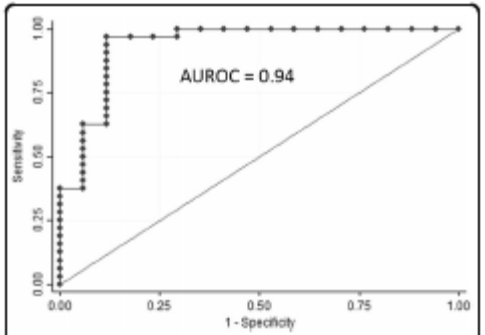
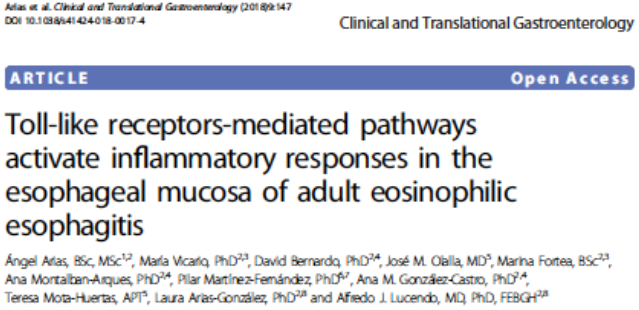


Fig. 4 Receiver operating curve for a salivary microbiome-based model including relative abundance of *Lautropia*, *Streptococcus*, and an unspecified genus of the order Bacteroidales. Area under the ROC = 0.94 (95% CI: 0.85–1.00) for the discrimination between BE and controls

Snider EJ. Clin Transl Gastroenterol 2018

Esophageal Microbiome



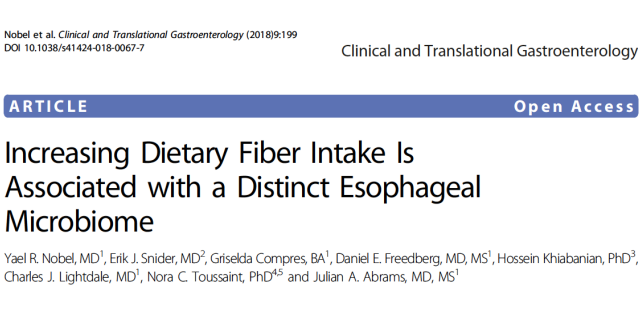
Arias et al. *Clinical and Translational Gastroenterology* (2018)9:147
DOI 10.1038/s41424-018-0017-4

Clinical and Translational Gastroenterology

ARTICLE Open Access

Toll-like receptors-mediated pathways activate inflammatory responses in the esophageal mucosa of adult eosinophilic esophagitis

Ángel Arias, BSc, MSc[1,2], María Vicario, PhD[2,3], David Bernardo, PhD[2,4], José M. Olalla, MD[5], Marina Fortea, BSc[2,3], Ana Montalban-Arques, PhD[2,4], Pilar Martínez-Fernández, PhD[6,7], Ana M. González-Castro, PhD[7,4], Teresa Mota-Huertas, APT[5], Laura Arias-González, PhD[2,8] and Alfredo J. Lucendo, MD, PhD, FEBGH[2,8]



Nobel et al. *Clinical and Translational Gastroenterology* (2018)9:199
DOI 10.1038/s41424-018-0067-7

Clinical and Translational Gastroenterology

ARTICLE Open Access

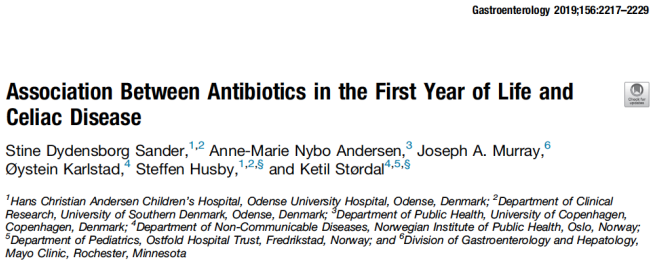
Increasing Dietary Fiber Intake Is Associated with a Distinct Esophageal Microbiome

Yael R. Nobel, MD[1], Erik J. Snider, MD[2], Griselda Compres, BA[1], Daniel E. Freedberg, MD, MS[1], Hossein Khiabanian, PhD[3], Charles J. Lightdale, MD[1], Nora C. Toussaint, PhD[4,5] and Julian A. Abrams, MD, MS[1]

Clinical & Translational Gastroenterology 2018

Clinical & Translational Gastroenterology 2018

Celiac Disease (the microbiome continued)



Gastroenterology 2019;156:2217–2229

Association Between Antibiotics in the First Year of Life and Celiac Disease

Stine Dydensborg Sander,[1,2] Anne-Marie Nybo Andersen,[3] Joseph A. Murray,[6] Øystein Karlstad,[4] Steffen Husby,[1,2,§] and Ketil Størdal[4,5,§]

[1]Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark; [2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark; [3]Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [4]Department of Non-Communicable Diseases, Norwegian Institute of Public Health, Oslo, Norway; [5]Department of Pediatrics, Ostfold Hospital Trust, Fredrikstad, Norway; and [6]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota

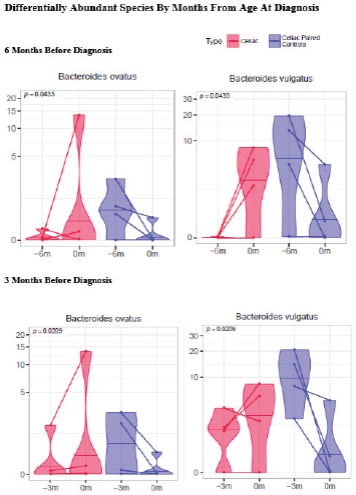
- Observational nation-wide register-based study
- All children
  - Denmark 1995 – 2012
  - Norway 2004– 2012
  - > 1.7 million children including 3346 with celiac
- Exposure to antibiotics in the first year of life linked with celiac disease (odds ratio 1.26)
- Implication that celiac is linked with alterations in the microbiome

Celiac Disease (the microbiome continued)

820

PROSPECTIVE LONGITUDINAL GUT METAGENOMIC ANALYSIS SUGGESTS ALTERED MICROBIOME COMPOSITION AND FUNCTION IN INFANTS PRIOR TO CELIAC DISEASE ONSET

Maureen M. Leonard, Poorani Subramanian, Francesco Valitutti, Gloria Serena, Victoria Kenyon, Stephanie Camhi, Pasquina Piemontese, Chiara Maria Trovato, Celeste Lidia Raguseo, Tiziana Passaro, Monica Montuori, Basilio Malamisura, Ruggero Francavilla, Luca Elli, Salvatore Cucchiara, Hiren Karathia, Rita Colwell, Nur A. Hasan, Alessio Fasano



DDW 2019

Celiac Disease

823

BENEFITS AND BARRIERS OF A HANDHELD CONSUMER GLUTEN DETECTOR AMONG ADULTS AND TEENAGERS WITH CELIAC DISEASE: A RANDOMIZED CLINICAL TRIAL.

Randi L. Wolf, Peter H. R. Green, Anne R. Lee, Norelle R. Reilly, Patricia Zybert, Benjamin Lebwohl

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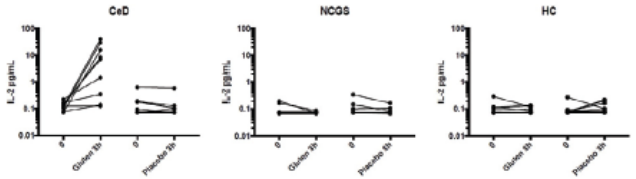
Celiac Disease

825

AN ACUTE RISE IN SERUM IL-2 LEVELS BUT NOT SYMPTOMS DIFFERENTIATES CELIAC DISEASE SUBJECTS FROM NON-CELIAC GLUTEN SENSITIVITY AND HEALTHY SUBJECTS IN A SINGLE DOSE RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED GLUTEN CHALLENGE

Amanda K. Cartee, Katherine S. King, Suyue Wang, John L. Dzuris, Robert P. Anderson, Carol T. Van Dyke, Chadrick A. Hinson, Eric Marietta, Rok Seon Choung, David A. Katzka, Vandana Nehra, Madhusudan Grover, Joseph A. Murray



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Conclusion

“It’s tough to make predictions, especially about the future”

- Yogi Berra

“I know of no way of judging the future but by the past”

- Patrick Henry

Thank you

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