

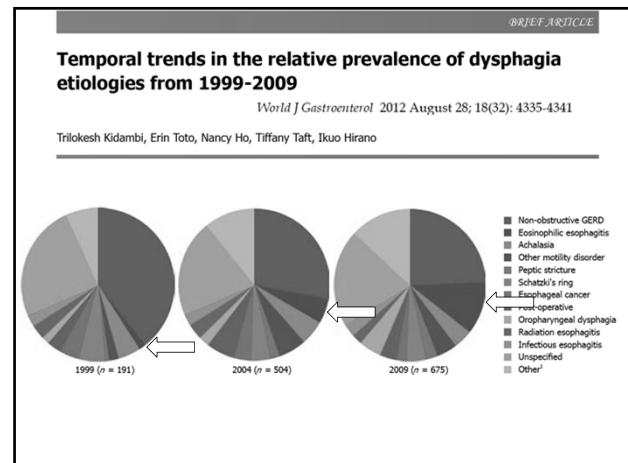
**Pediatric
Eosinophilic Esophagitis
Research:
Where are We Going?**

North American Society of Pediatric Gastroenterology,
Hepatology and Nutrition

Annual Meeting
October 26, 2014

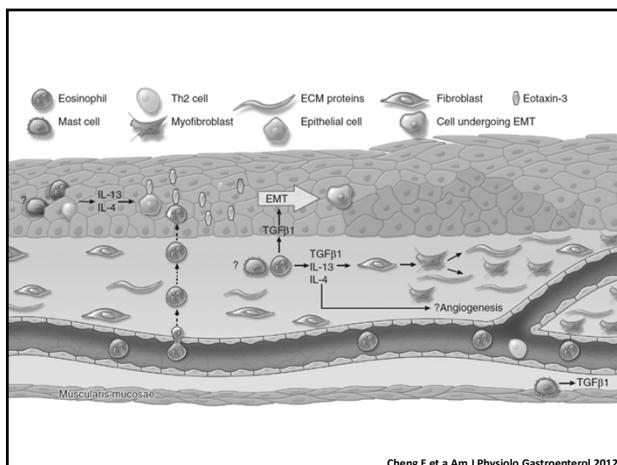
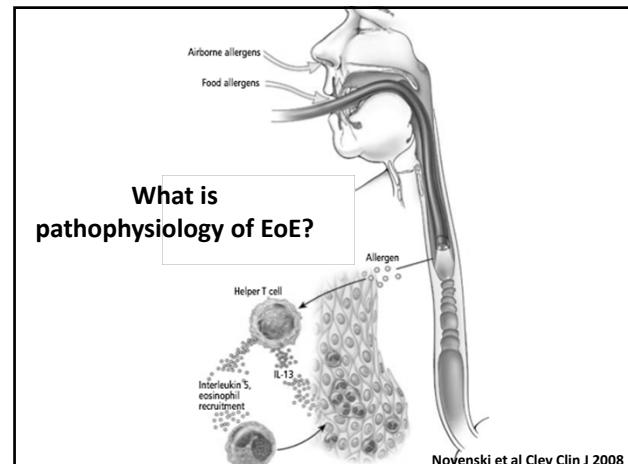
Glenn T. Furuta
Digestive Health Institute
Children's Hospital Colorado, Aurora, CO
Gastrointestinal Eosinophilic Diseases Program
University of Colorado School of Medicine





In the last year, have we,

- Identified Novel Therapeutic Targets?
- Improved Therapeutic Strategies?
- Developed New Assessment Tools?



Helicobacter

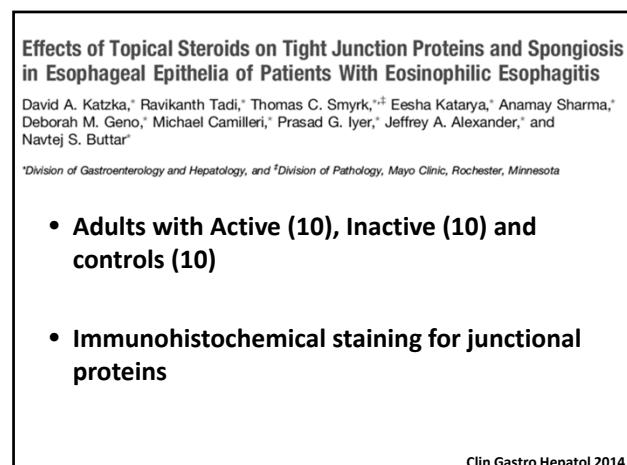
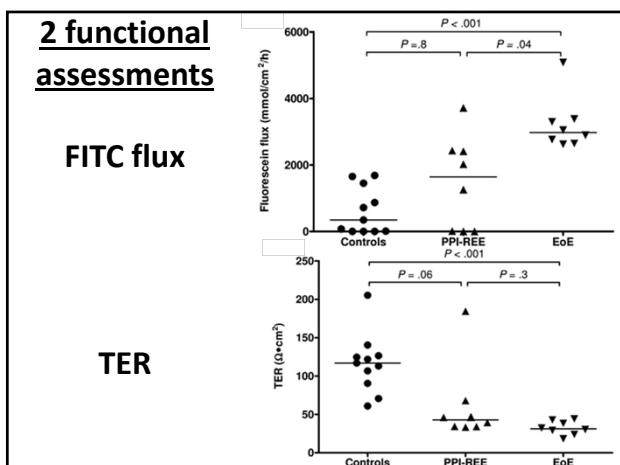
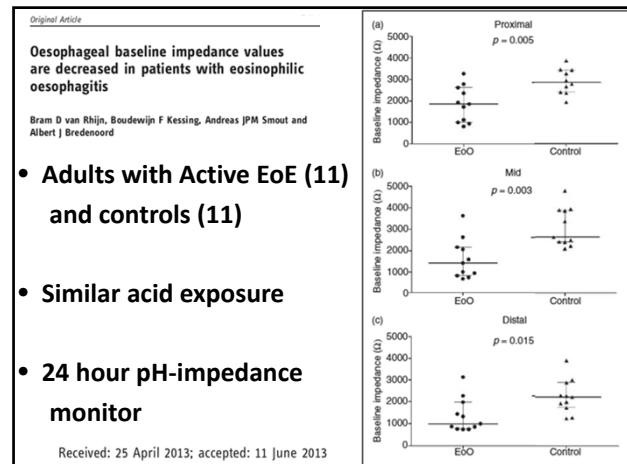
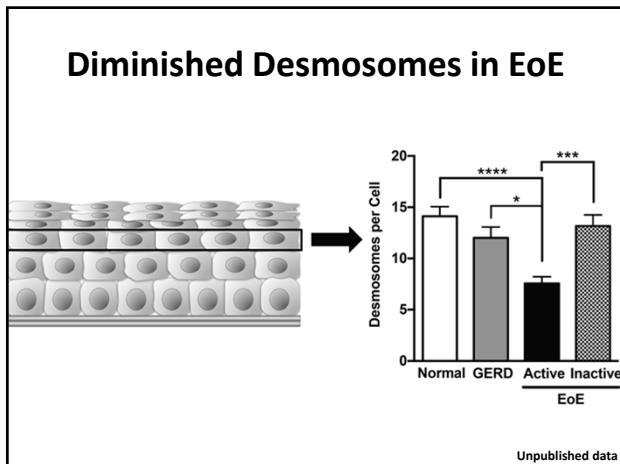
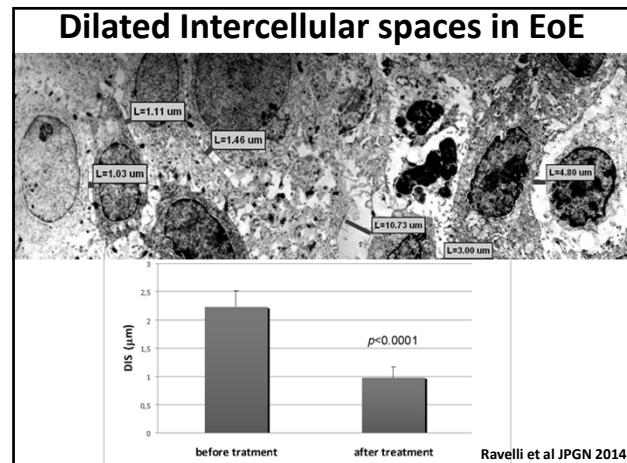
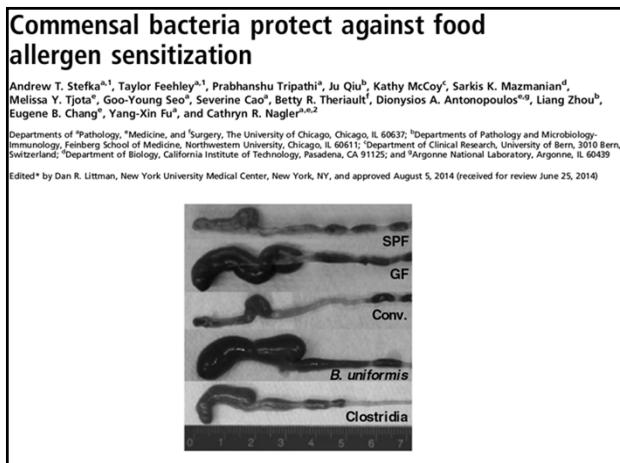
Helicobacter ISSN 1523-5378
doi: 10.1111/hel.12129

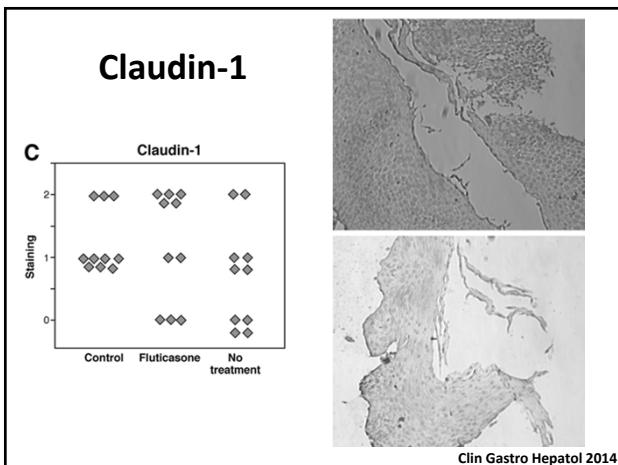
Does *Helicobacter pylori* Protect against Eosinophilic Esophagitis in Children?

Yoram Elitsur,* Baraa Alabd Alrazzak,* Deborah Preston* and Yulia Demetieva†

*Gastroenterology Division, Department of Pediatrics, Marshall University School of Medicine, Huntington, WV, USA, †Department of Mathematics, Emmanuel College, Boston, MA, USA

- Retrospective review of children's first endoscopy
- 966 charts
 - 62 with EoE
 - 31 with HP
- Significant negative relationship between Hp and EoE



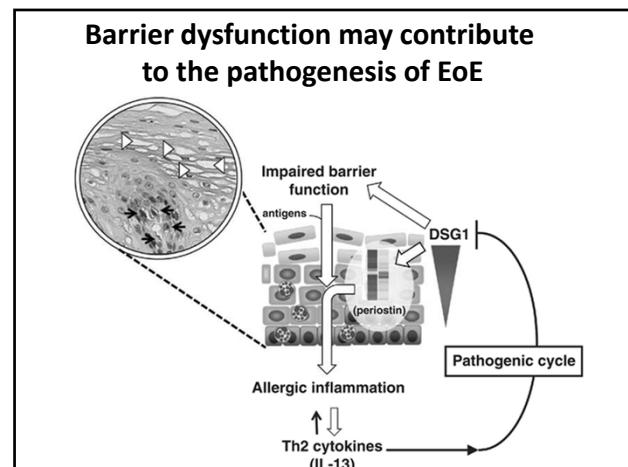
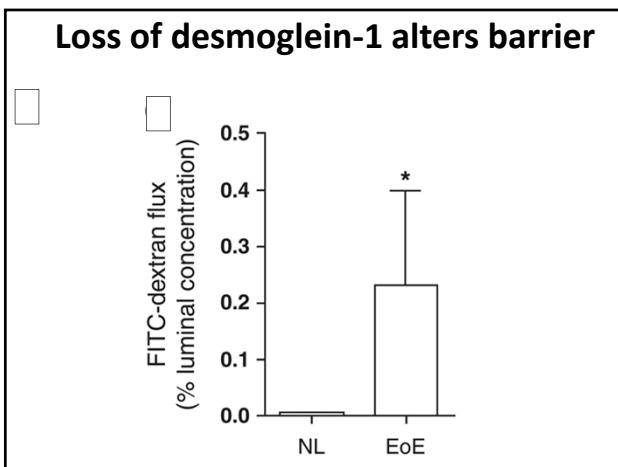
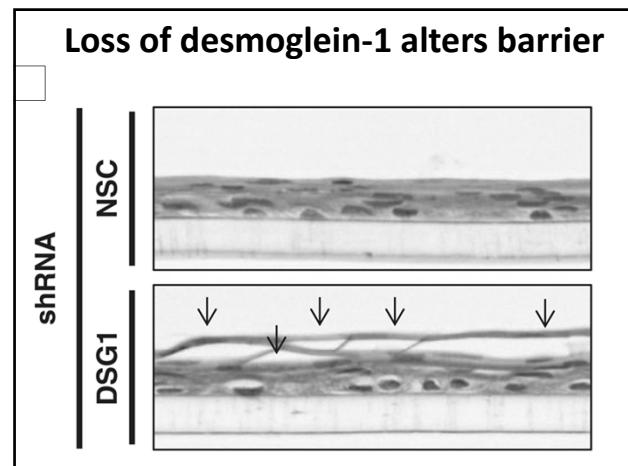
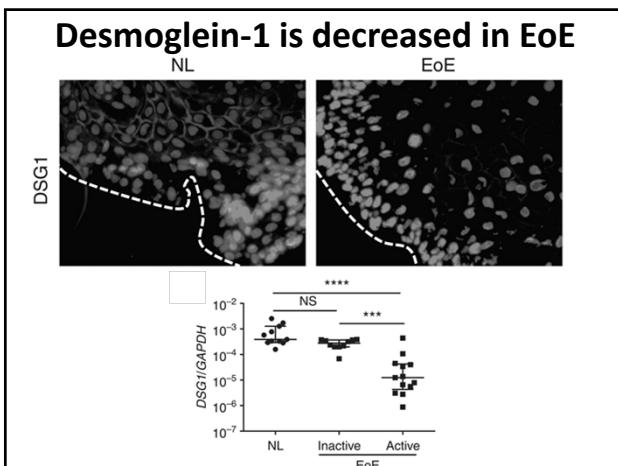


Desmoglein-1 regulates esophageal epithelial barrier function and immune responses in eosinophilic esophagitis

JD Sherrill¹, K KC¹, D Wu¹, Z Djukic², JM Caldwell¹, EM Stucke¹, KA Kemme¹, MS Costello¹, MK Mingler¹, C Blanchard³, MH Collins⁴, JP Abonia¹, PE Putnam⁵, ES Dellon², RC Orlando^{2,6}, SP Hogan¹ and ME Rothenberg¹

Mucosal Immunology

13 November 2013. doi:10.1038/mi.2013.90



published online 13 July 2014; doi:10.1038/ng.3033

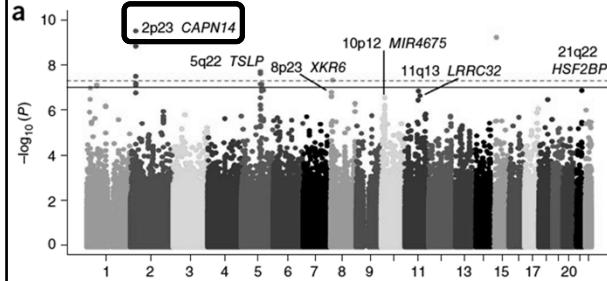
Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease

Leah C Kottyan^{1-3,13}, Benjamin P Davis^{3,13}, Joseph D Sherrill³, Kan Liu³, Mark Rochman³, Kenneth Kaufman^{1,2}, Matthew T Weirauch^{1,4}, Samuel Vaughn¹, Sara Lazar^{1,2}, Andrew M Rupert⁴, Mojtaba Kohram⁴, Emily M Stucke³, Katherine A Kemme³, Albert Magnusen^{1,2}, Hua He⁵, Phillip Dexheimer⁴, Mirna Chehade⁶, Robert A Wood⁷, Robbie D Pesek⁸, Brian P Vickery⁹, David M Fleischer¹⁰, Robert Lindbad¹¹, Hugh A Sampson⁶, Vincent A Mukkada¹², Phil E Putnam¹², J Pablo Abonia³, Lisa J Martin⁵, John B Harley^{1,2,14} & Marc E Rothenberg^{3,14}

29 PhD and MD scientists
6 different academic institutions
almost 10,000 patients

Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease

Leah C Kottyan^{1-3,13}, Benjamin P Davis^{3,13}, Joseph D Sherrill³, Kan Liu³, Mark Rochman³, Kenneth Kaufman^{1,2}, Matthew T Weirauch^{1,4}, Samuel Vaughn¹, Sara Lazar^{1,2}, Andrew M Rupert⁴, Mojtaba Kohram⁴, Emily M Stucke³, Katherine A Kemme³, Albert Magnusen^{1,2}, Hua He⁵, Phillip Dexheimer⁴, Mirna Chehade⁶, Robert A Wood⁷, Robbie D Pesek⁸, Brian P Vickery⁹, David M Fleischer¹⁰, Robert Lindbad¹¹, Hugh A Sampson⁶, Vincent A Mukkada¹², Phil E Putnam¹², J Pablo Abonia³, Lisa J Martin⁵, John B Harley^{1,2,14} & Marc E Rothenberg^{3,14}

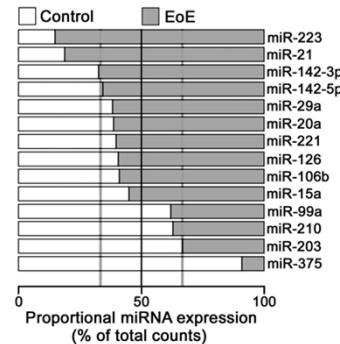


miR 223

- Leukocyte proliferation and activation
- Cytokine production
- Target genes involved in adaptive immune system polarization
- Regulation of eotaxin-3

Lu TX et al JACI 2012

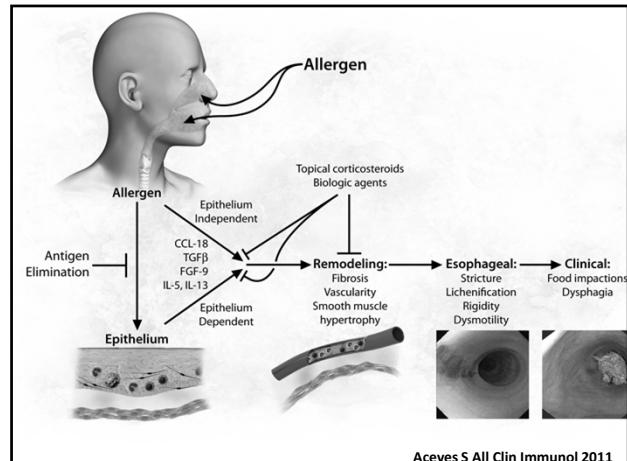
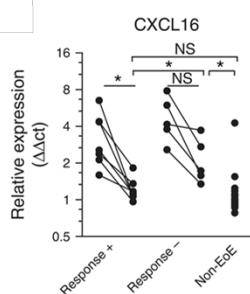
miR expression in EoE



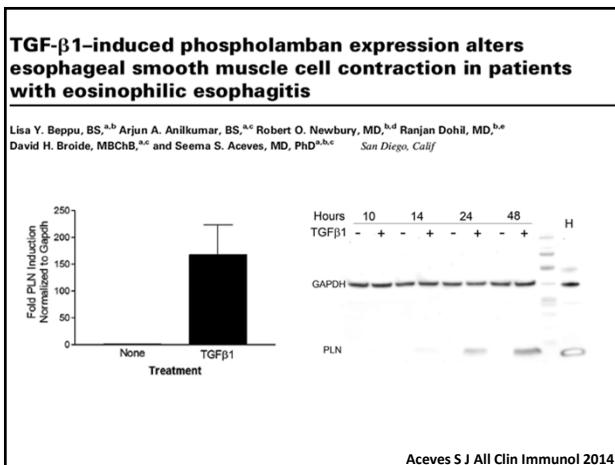
Zahn AM, Menard-Katcher C et al Am J Physiol Gastrointest Liver Physiol 2014

Involvement of the iNKT Cell Pathway Is Associated With Early-Onset Eosinophilic Esophagitis and Response to Allergen Avoidance Therapy

Willem S. Lexmond, MD¹, Joana F. Neves, PhD², Samuel Nurko, MD, MPH¹, Torsten Olszak, MD², Mark A. Exley, PhD², Richard S. Blumberg, MD^{2,3} and Edda Fischer, PhD^{3,4}
11 February 2014; doi:10.1038/ajg.2014.12



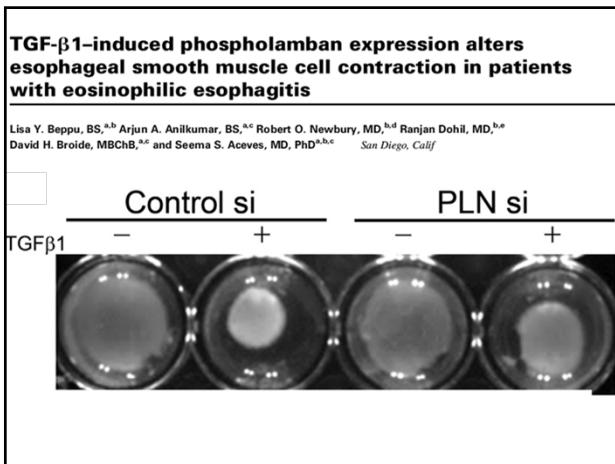
Aceves S All Clin Immunol 2011



TGF- β 1-induced phospholamban expression alters esophageal smooth muscle cell contraction in patients with eosinophilic esophagitis

Lisa Y. Beppu, BS,^{a,b} Arjun A. Anilkumar, BS,^{a,c} Robert O. Newbury, MD,^{b,d} Ranjan Dohil, MD,^{b,e} David H. Broide, MBChB,^{a,c} and Seema S. Aceves, MD, PhD^{a,b,c} San Diego, Calif

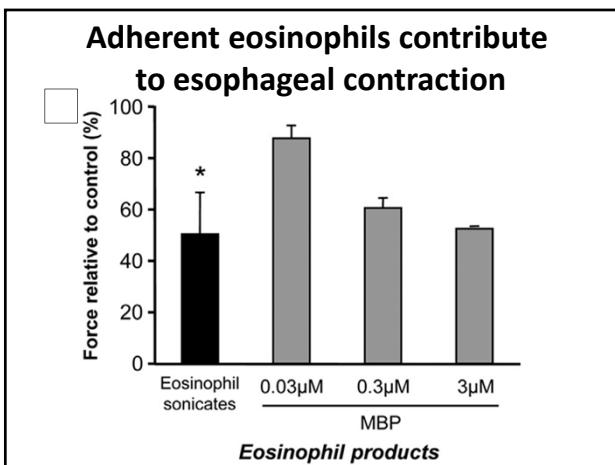
- Phospholamban is a protein associated with tissue contraction
 - Required for cardiac contraction
 - Present in gastric smooth muscle
 - Associated with gallbladder contraction
 - Reduced in colitis



Gastroenterology 2014;146:1266-1277
BASIC AND TRANSLATIONAL—ALIMENTARY TRACT

T-Helper 2 Cytokines, Transforming Growth Factor β 1, and Eosinophil Products Induce Fibrogenesis and Alter Muscle Motility in Patients With Eosinophilic Esophagitis

Florian Rieder,^{1,2} Ilche Nonevski,¹ Jia Ma,³ Zhufeng Ouyang,¹ Gail West,² Cheryl Protheroe,⁴ Giovanni DePetris,⁵ Anja Schirbel,² James Lapinski,⁶ John Goldblum,⁶ Tracey Bonfield,⁷ Rocio Lopez,⁸ Karen Harnett,³ James Lee,⁴ Ikuro Hirano,⁹ Gary Falk,¹ Piero Biancani,³ and Claudio Fiocchi^{1,2}



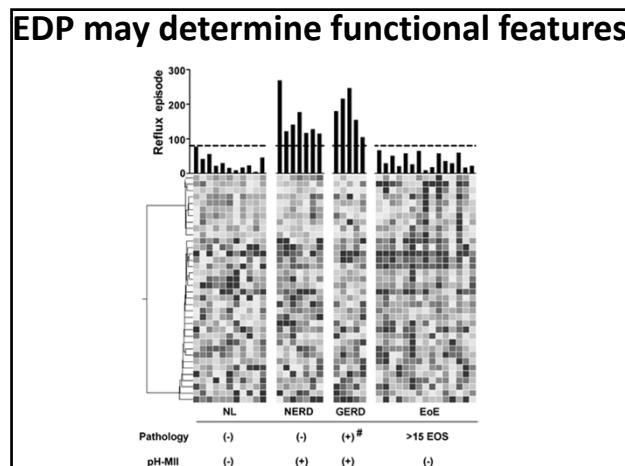
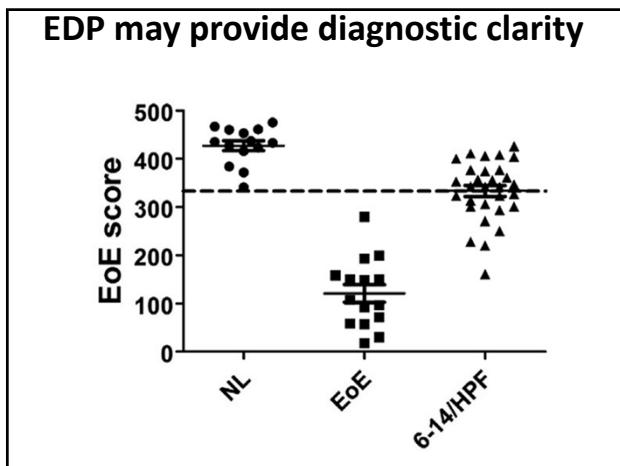
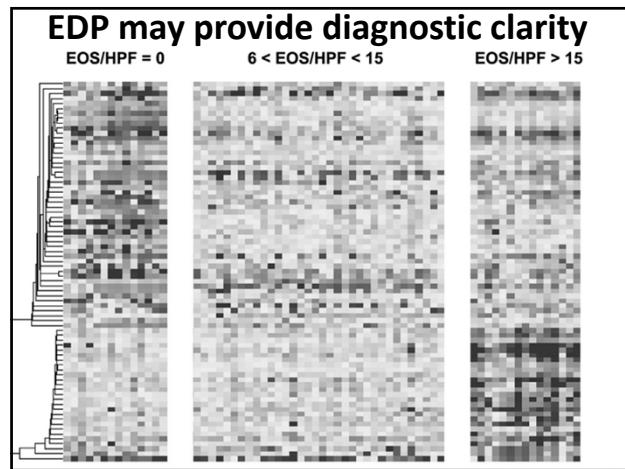
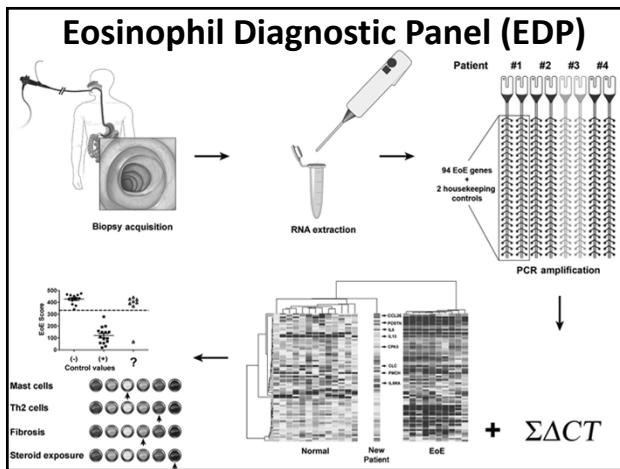
GASTROENTEROLOGY 2013;145:1289-1299
BASIC AND TRANSLATIONAL—ALIMENTARY TRACT

Molecular Diagnosis of Eosinophilic Esophagitis by Gene Expression Profiling

TING WEN,¹ EMILY M. STUCKE,¹ TOMMIE M. GROTJAN,¹ KATHERINE A. KEMME,¹ J. PABLO ABONIA,¹ PHILIP E. PUTNAM,² JAMES P. FRANCIOSI,³ JOSE M. GARZA,⁴ AJAY KAUL,⁵ EILEEN C. KING,⁶ MARGARET H. COLLINS,⁷ JONATHAN P. KUSHNER,⁸ and MARC E. ROTHEMBERG¹

¹Division of Allergy and Immunology; ²Division of Gastroenterology, Hepatology and Nutrition; ³Department of Pediatrics; ⁴Division of Pediatric Pathology, Cincinnati Children's Hospital Medical Center; and ⁵Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio

Eosinophil Diagnostic Panel (EDP)



AP&T Alimentary Pharmacology and Therapeutics

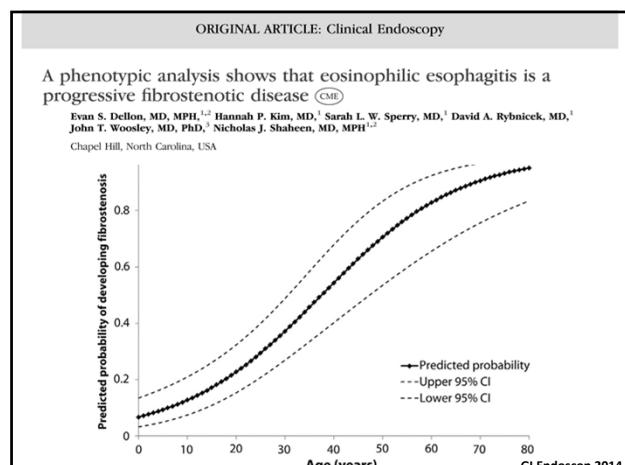
The natural history of eosinophilic oesophagitis in the transition from childhood to adulthood

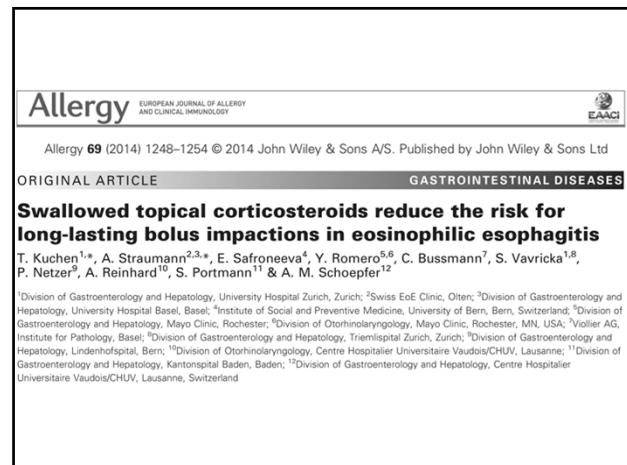
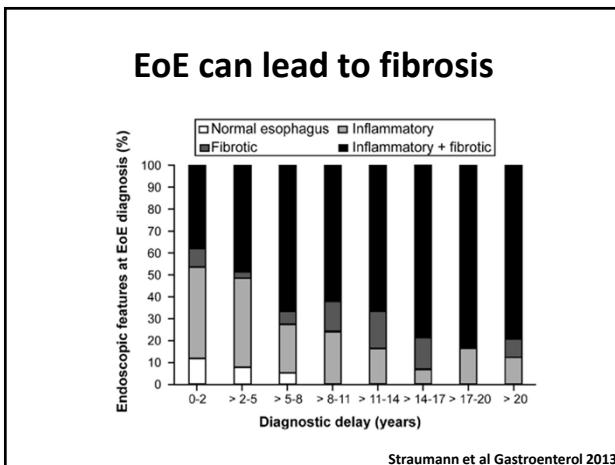
P. Menard-Katcher*, K. L. Marks†, C. A. Liacouras‡, J. M. Spergel†§, Y.-X. Yang*¶ & G. W. Falk*

Aliment Pharmacol Ther 2013; 37: 114-121

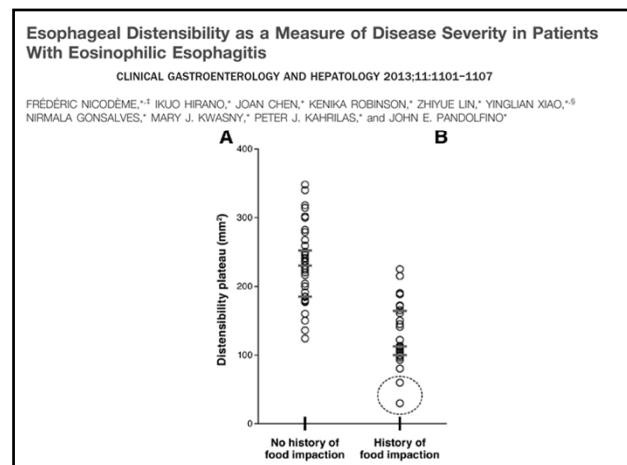
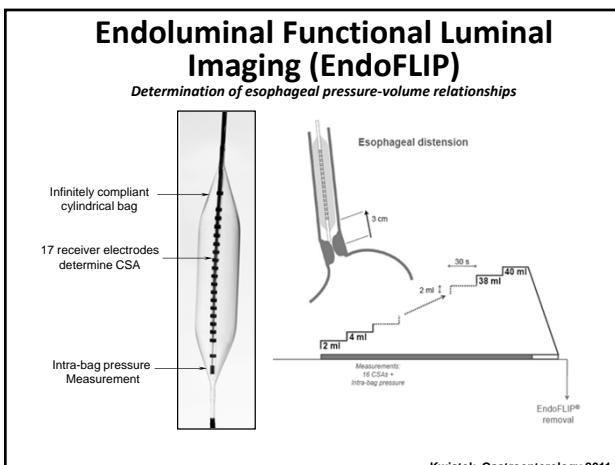
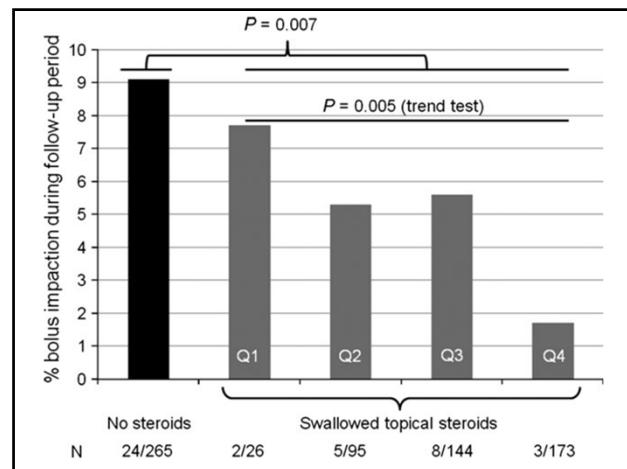
Conclusions

The majority of young adults diagnosed with EoE during childhood continue to require pharmacological treatment and/or dietary modification for EoE. A substantial proportion of this population experiences ongoing swallowing difficulties that a standard dysphagia questionnaire fails to capture. Dietary quality of life, but not total quality of life, appears to be adversely affected. These data suggest that EoE diagnosed during childhood remains a significant medical issue during early adulthood, and that better EoE symptom measurement instruments are needed.



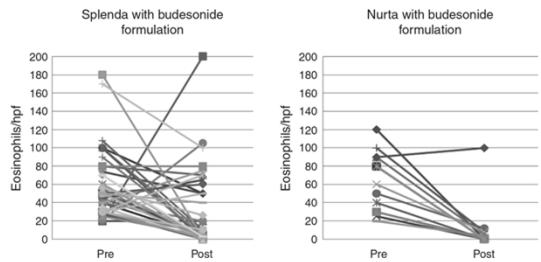


- Retrospective study
- 206 patients with 5 year follow up
- 33 patients with 42 impactions
- Esophageal stricture-OR 2.666, 95% CI, 1.259-5.465, p=0.01
- Increased frequency of TCS reduced risk of FI



Comparison of 2 Delivery Vehicles for Viscous Budesonide to Treat Eosinophilic Esophagitis in Children

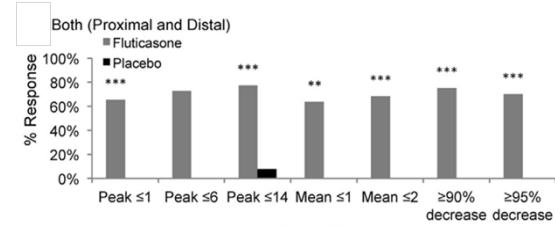
*Eitan Rubinstein, *John J. Lee, *Ari Fried, †Tanya Logvinenko, *Peter Ngo, †Douglas McDonald, and *Elizabeth J. Halt



Efficacy, Dose Reduction, and Resistance to High-Dose Fluticasone in Patients With Eosinophilic Esophagitis

Bridget K. Butz,^{1,*} Ting Wen,^{1,*} Gerald J. Gleich,² Glenn T. Furuta,³ Jonathan Spergel,⁴ Eileen King,⁵ Robert E. Kramer,³ Margaret H. Collins,⁶ Emily Stucke,¹ Colleen Mangeot,⁵ W. Daniel Jackson,⁷ Molly O'Gorman,⁷ J. Pablo Abonia,¹ Scott Pentiuk,⁸ Philip E. Putnam,⁸ and Marc E. Rothenberg¹

Gastroenterology 2014;147:324–333



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- 22 treated, 13 placebo, 1760 mcg daily dose

- No differences in severity or frequency of symptoms

- 1 subject developed thrush

- 8 subjects with decreased cortisol

Box 1 Original classification and grading system for the endoscopic assessment of the oesophageal features of eosinophilic oesophagitis

EREFs- Edema Rings Exudates Furrows Stricture

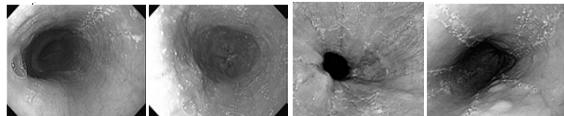
- Major features**
- **Fixed rings** (also referred to as concentric rings, corrugated oesophagus, corrugated rings, ringed oesophagus, trachealization)
 - Grade 0: none
 - Grade 1: mild (stable circumferential ridges)
 - Grade 2: moderate (distinct rings that do not impair passage of a standard diagnostic adult endoscope (tube diameter 8–9.5 mm))
 - Grade 3: severe (distinct rings that do not permit passage of a diagnostic endoscope)
 - **Exudates** (also referred to as white spots, plaques)
 - Grade 0: none
 - Grade 1: mild (lesions involving <10% of the oesophageal surface area)
 - Grade 2: severe (lesions involving >10% of the oesophageal surface area)
 - **Furrows** (also referred to as vertical lines, longitudinal furrows)
 - Grade 0: absent
 - Grade 1: mild (vertical lines present without visible depth)
 - Grade 2: severe (vertical lines with mucosal depth (indentation))
 - **Oedema** (also referred to as decreased vascular pattern, mucosal pallor)
 - Grade 0: absent (distinct vascular pattern)
 - Grade 1: mild (loss of clarity of vascular markings)
 - Grade 2: severe (absence of vascular markings)
 - **Stricture**
 - Grade 0: absent
 - Grade 1: present

Hirano et al
Gut May 2012

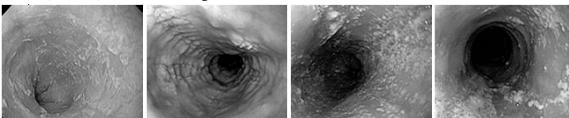
Reference for Endoscopic Abnormalities (EoE-EREFs)

Exudates (Also referred to as white exudates, plaques or punctate white spots)

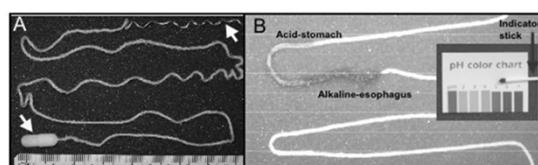
Mild (Grade 1): Scattered lesions occupying <10% of the surface area of the



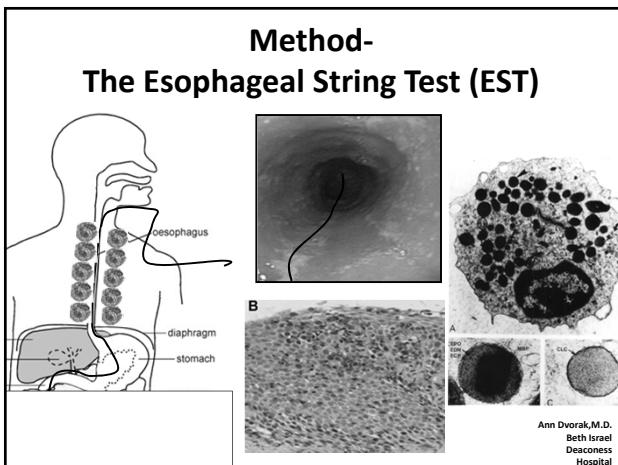
Severe (Grade 2): Lesions involving ≥ 10% of the surface area of the



The Enterotest



Developed in 1970's for analysis of
parasitic infections



Accuracy, Safety, and Tolerability of Tissue Collection by Cytosponge vs Endoscopy for Evaluation of Eosinophilic Esophagitis

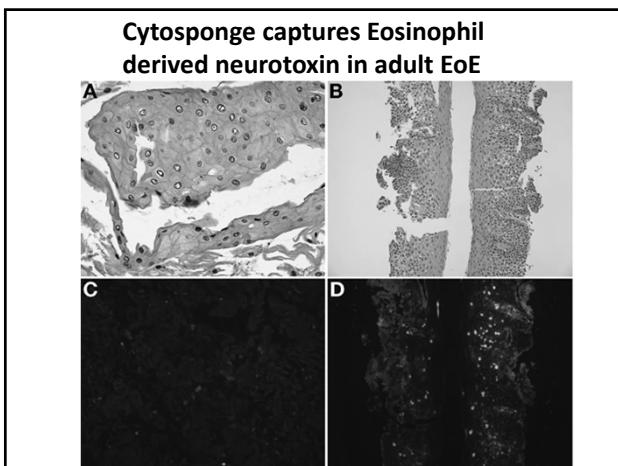
David A. Katzka,¹ Debra M. Geno,¹ Anupama Ravi,² Thomas C. Smyrk,³ Pierre Lao-Sirieix,¹ Ahmed Miramedi,¹ Irene Debiram,¹ Maria O'Donovan,⁴ Hirohito Kita,² Gail M. Kephart,² Lori A. Kryzer,² Michael Camilleri,¹ Jeffrey A. Alexander,¹ and Rebecca C. Fitzgerald¹

¹Division of Gastroenterology and Hepatology, ²Division of Pulmonary Medicine, and ³Department of Pathology, Mayo Clinic Rochester, Minnesota; ⁴MRC Cancer Unit, Hutchinson/MRC Research Centre, University of Cambridge, Cambridge, United Kingdom, and ⁵Department of Pathology, Addenbrooke's Hospital, Cambridge University NHS Foundation Trust, Cambridge, United Kingdom



Fig 1 | Cytosponge in gelatin capsule (right) and expanded (left)

Courtesy of David Katzka and Rebecca Fitzgerald

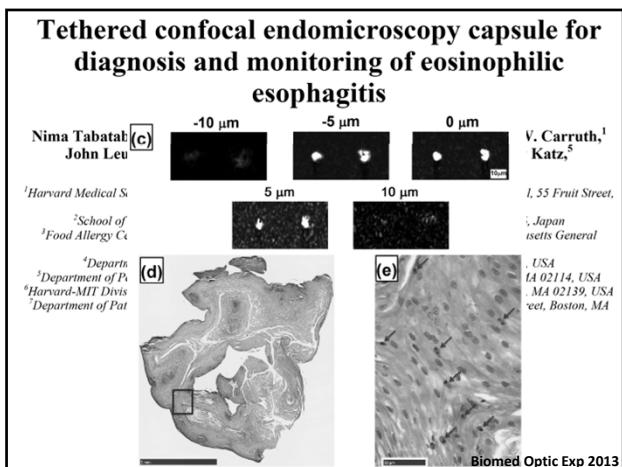
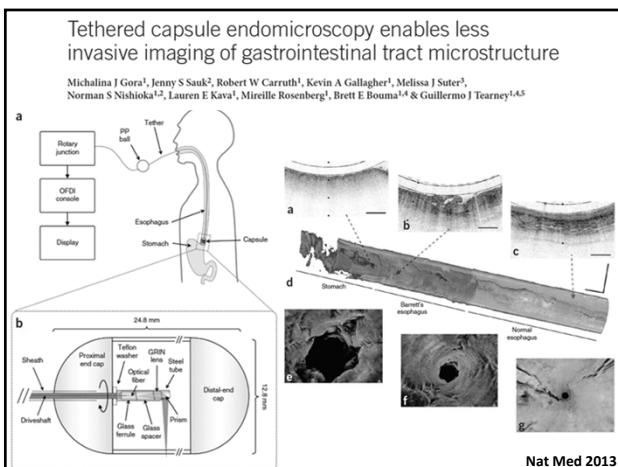


Tethered capsule endomicroscopy enables less invasive imaging of gastrointestinal tract microstructure

Michalina J Gora¹, Jenny S Sauk², Robert W Carruth¹, Kevin A Gallagher¹, Melissa J Suter³, Norman S Nishioka^{1,2}, Lauren E Kava¹, Mireille Rosenberg¹, Brett E Bouma^{1,4} & Guillermo J Tearney^{1,4,5}

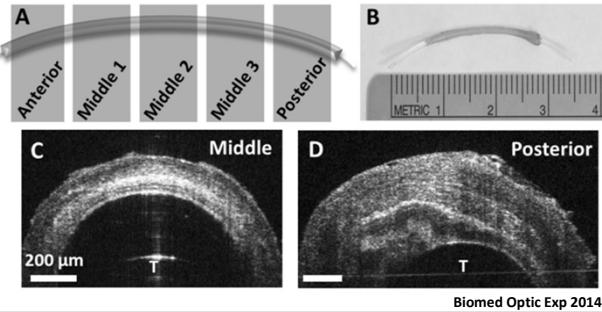
NATURE MEDICINE ADVANCE ONLINE PUBLICATION

13 January 2013; doi:10.1038/nm.3052



Characterization of eosinophilic esophagitis murine models using optical coherence tomography

Aneesh Alex,^{1,2} Mario Noti,^{3,4,5} Eli D. Tair Wojno,^{3,4,5} David Artis,^{3,4,5} and Chao Zhou,^{1,2,6*}



Biomed Optic Exp 2014

Ron Sokol

Colleagues in Digestive Health Institute
Children's Hospital Colorado
University of Colorado School of Medicine



National Institutes of Health, CTSA, FDA
American Gastroenterological Association, APFED, Pappas Foundation, CURED, FARE

