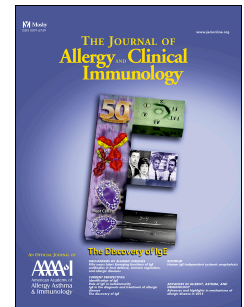


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New Developments in Eosinophilic Gastrointestinal Diseases Presented at the
CEGIR/TIGERS Symposium at the 2018 AAAAI Meeting

Jonathan M. Spergel, MD, PhD, Seema S. Aceves, MD, PhD, Kara Kliewer, PhD,
Nimi Gonsalves, MD, Mirna Chehade, MD, Joshua B. Wechsler, MD, PhD, Marion
Groetch, MS, Joshua Friedlander, DO, Evan S. Dellon, MD, MPH, Wendy Book, MD,
Ikuo Hirano, MD, Amanda B. Muir, MD, Antonella Cianferoni, MD, PhD, Lisa Spencer,
PhD, Chris A. Liacouras, MD, Edaire Cheng, MD, PhD, Leah Kottyan, PhD, Ting
Wen, MD, PhD, Thomas Platts-Mills, MD, PhD, Marc E. Rothenberg, MD, PhD



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Jonathan M. Spergel^{*1,2}, MD, PhD, Seema S. Aceves^{*3}, MD, PhD, Kara Kliewer⁴, PhD, Nimi
Gonsalves⁵, MD, Mirna Chehade, MD⁶, Joshua B. Wechsler, MD, PhD⁷, Marion Groetch, MS⁶,
Joshua Friedlander, DO⁸, Evan S. Dellon, MD, MPH⁹, Wendy Book, MD¹⁰, Ikuo Hirano, MD⁵,
Amanda B. Muir^{2,11}, MD, Antonella Cianferoni^{1,2}, MD, PhD, Lisa Spencer¹², PhD, Chris A.
Liacouras^{2,11}, MD, Edaire Cheng¹³, MD, PhD, Leah Kottyan⁴, PhD, Ting Wen⁴, MD, PhD,
Thomas Platts-Mills¹⁴, MD, PhD, Marc E. Rothenberg⁴, MD, PhD

¹Division of Allergy and Immunology, The Children's Hospital of Philadelphia, PA, USA

²Department of Pediatrics, The Perelman School of Medicine, University of Pennsylvania;

³Division of Allergy, Immunology, Departments of Pediatrics and Medicine, University of

California, San Diego, Rady Children's Hospital, San Diego, La Jolla CA; ⁴Division of Allergy

and Immunology, Cincinnati Children's Hospital Medical Center and Department of Pediatrics,

University of Cincinnati, Cincinnati, OH; ⁵Division of Gastroenterology and Hepatology,

Northwestern University – Feinberg School of Medicine, Chicago, IL; ⁶Mount Sinai Center for

Eosinophilic Disorders, Icahn School of Medicine at Mount Sinai, New York, NY, USA;

⁷Eosinophilic Gastrointestinal Diseases Program, Division of Gastroenterology, Hepatology, and

Nutrition, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; ⁸Digestive

Health Institute, Children's Hospital Colorado, Aurora, CO; Aerodigestive Program, University

of Colorado School of Medicine, Aurora, CO; ⁹Center for Esophageal Diseases and Swallowing,

Division of Gastroenterology and Hepatology, University of North Carolina School of Medicine,
Chapel Hill, NC, USA; ¹⁰American Partnership for Eosinophilic Disorders, Atlanta, GA, United
States; ¹¹Division of Gastroenterology and Nutrition, The Children's Hospital of Philadelphia,
PA, USA; ¹²Beth Israel Deaconess, Boston, MA; ¹³Departments of Pediatrics and Internal
Medicine, Children's Medical Center, University of Texas Southwestern Medical Center, Dallas,
Texas, USA; ¹⁴Division of Asthma, Allergy, and Immunology, University of Virginia,
Charlottesville, VA, USA

*Co-First Authors

Corresponding Author:

Marc E. Rothenberg, MD, PhD

Cincinnati Children's Hospital Medical Center

Cincinnati, OH

Rothenberg@cchmc.org

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Abbreviations

AAAAI	American Academy of Allergy, Asthma & Immunology
AGREE	A working Group on PPI-REE
APFED	American Partnership for Eosinophilic Disorders
BZH	basal zone hyperplasia
CAPN14	calpain 14
CD4	cluster of differentiation 4
CEGIR	Consortium of Eosinophilic Gastrointestinal Disease Researchers
EC	eosinophilic colitis
EDP	EoE Diagnostic Panel
EG	eosinophilic gastritis
EGE	eosinophilic gastroenteritis
EGIDs	eosinophilic gastrointestinal diseases
EoE	eosinophilic esophagitis
EoEe1	EoE endotype 1 (EDP identified)
EoEe2	EoE endotype 2 (EDP identified)
EoEe3	EoE endotype 3 (EDP identified)
EST	Esophageal String Test
FDA	US Food and Drug Administration
GERD	gastroesophageal reflux disease
IgE	immunoglobulin E
IgG	immunoglobulin G

68	IgG4	immunoglobulin G4
69	IL	interleukin
70	iNKT	invariant natural killer cells
71	PPI	proton pump inhibitor
72	PPI-REE	proton pump inhibitor–responsive esophageal eosinophilia
73	SNP	single-nucleotide polymorphism
74	Th2	T helper type 2
75	TIGER	The International Gastrointestinal Eosinophil Researchers
76	TNE	transnasal endoscopy
77	TSLP	thymic stromal lymphopoietin
78	WAO	World Allergy Organization

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ACCEPTED MANUSCRIPT

The Consortium of Eosinophilic Gastrointestinal Diseases (CEGIR), along with The International Gastrointestinal Eosinophil Researchers (TIGER) organized a day-long symposium at the recent 2018 annual meeting of the American Academy of Allergy, Asthma, and Immunology (AAAAI), which was coupled for the first time with the World Allergy Organization (WAO) meeting to create an international platform. The symposium featured experts in many facets of eosinophilic gastrointestinal diseases (EGIDs), including allergy, immunology, gastroenterology, pathology, and nutrition and was a well-attended event. The basic science, genetics, cellular immunology, and clinical features of the diseases, with a focus on epithelial, eosinophil, and mast cell responses, as well as current and emerging treatment options, were reviewed.¹ Herein, we will briefly review some of the highlights of the material presented at the meeting.

Conflict of Interest

Dr. Spergel reports grants from NIH, End Allergy Together and Aimmune Therapeutics; grants and personal fees from Regeneron, Shire, and DBV Technology; personal fees from UpToDate, Abbott, and Annuals of Allergy Asthma and Immunology, outside the submitted work. Dr. Aceves reports a grant from NIH and a UCSD patented licensed to Shire Pharma. Dr. Chehade reports receiving grants from NIH, PCORI, Nutricia, Regeneron and Shire; and consulting fees from Allakos, and Shire. Marion Groetch has received honoraria from Abbott, Nutricia North America and Mead Johnson for educational lectures. Dr. Friedlander reports personal fees and other from Triple Endoscopy, Inc; grants from CURED Foundation, OEDIT-STATE of Colorado; in addition, Dr. Friedlander has a patent on Pediatric Nasal Endoscope/Aerodigestive

Scope with royalties paid to University of Colorado. Dr. Dellon reports grants and personal fees from Adare, Banner, Celgene/Receptos, Regeneron, Shire; personal fees from Alivio, Allakos, AstraZeneca, Enumeral, Robarts Clinical Trials; grants from Meritage, Miraca, Nutricia, and Holoclara. Dr. Hirano reports grants and consultant fees from Adare, Shire, Regeneron, and Receptos. Dr. Cianferoni reports grants and personal fees from DBV and grants from Shire. Dr. Cheng reports personal fees from Abbott Nutrition. Dr. Kottyan reports a pending patent WO2015142739A1. Drs. Wen and Rothenberg are co-inventors of issued and pending patents owned by CCHMC. Dr. Rothenberg reports grants from NIH; US-Israel Binational Grant, and PCORI; personal fees from Celgene and Genetech; equity in Immune Pharmaceuticals, PulmOne, and Spoon Guru and personal fees from Glaxo Smith Kline, Merck, Allakos, AstraZeneca, Celgene and Regeneron; in addition, Dr. Rothenberg receives royalties from UpToDate and reslizumab (Teva Pharmaceuticals). All other authors have nothing to disclose.

Epidemiology of EGIDs. The knowledge related to the epidemiology of eosinophilic gastritis (EG), gastroenteritis (EGE), and colitis (EC) remains limited. The prevalence of these conditions ranges from 3.5 to 8.3 per 100,000, with approximately 50,000 cases total estimated in the U.S.² There does not appear to be a male predominance, but there is an association with atopy. No etiologic or risk factor studies have been done for EG, EGE, or EC. The epidemiology of eosinophilic esophagitis (EoE) is far better described.³ The prevalence is approximately 1 per 2000, with an estimated 150,000 cases in the U.S. and large burden of disease (>\$1 billion annually).^{4, 5} Both the incidence and prevalence of EoE are increasing rapidly, and there is much research interest in these evolving trends. Though no specific “cause” for the rise in increase has been found, there are a number of potential risk factors, including the decrease of *Helicobacter pylori* infection, low population density, and early life exposures such as antibiotic use.⁶ Gene-environment interactions, particularly between breastfeeding and single-nucleotide polymorphisms in *CAPN14*, have recently been identified as a predisposing factor.⁷ EoE is a highly atopic disease with a high rate of asthma, allergic rhinitis, and IgE-mediated food allergy. For food allergy, it is also known that oral immunotherapy might induce EoE in about 5% of cases.⁸

Consequences of EoE: Remodeling. Unbridled Th2 eosinophilic esophageal inflammation leads to esophageal rigidity in children and adults via tissue remodeling that includes histologic changes of basal zone hyperplasia, fibrosis, angiogenesis and smooth muscle hyperplasia with hypertrophy.^{9, 10} Current data in adults demonstrate that uncontrolled EoE can result in a fibrostenotic state with resultant strictures in the majority of patients.^{11, 12} The use of endoscopic functional lumen imaging probe technology provides a novel esophageal readout for compliance

and motility.^{13, 14} A rigid extracellular matrix has consequences in terms of both esophageal biomechanics and structural cell function.^{15, 16} Esophageal fibroblasts cultured on a rigid matrix have increased contractility and myofibroblast features, and smooth muscle cells become hypertrophic and have increased expression of contractility and fibrotic genes when cultured in a stiff matrix.^{15, 16} Therapies that reduce inflammation in children and adults can reverse histologic fibrosis and esophageal rigidity in a subset of subjects.^{17, 18} A future direction for EoE therapy will be to treat not only inflammation, but also the complications of dysfunctional esophageal biomechanics.

Relationship Between EoE and Other Forms of Esophagitis with Focus on Proton Pump

Inhibitor (PPI) Responses. EoE and gastroesophageal reflux disease (GERD) share a complex relationship, and previous assumptions used to dichotomize the two may be flawed.^{19, 20} PPI-responsive esophageal eosinophilia (PPI-REE) describes patients that have esophageal eosinophilia; typical EoE symptoms, endoscopic features, and histology; and no evidence of GERD by endoscopy but exhibit clinical and histologic response to PPIs. There is still controversy surrounding the entity and the extent to which it overlaps with, or is a sub-type of, EoE.^{21, 22} Clinically, a number of conditions can cause esophageal eosinophilia. However, when patients present with typical symptoms of esophageal dysfunction, atopy, endoscopic findings suggestive of EoE, and biopsies with marked esophageal eosinophilia, they appear to have EoE. There are now extensive data that suggest the clinical, endoscopic, histologic, immunologic, and molecular features of these patients at baseline (before PPI treatment) are largely indistinguishable between PPI responders (PPI-REE) and non-responders (classic EoE).^{4, 21-23} One possible mechanism for PPI-REE is that patients with EoE respond to anti-inflammatory

effects of PPIs unrelated to gastric acid inhibition. PPIs have been documented to induce histologic remission in ~50% of patients with symptomatic esophageal eosinophilia, block Th2 cytokine-induced eotaxin-3 secretion in esophageal (and bronchial) epithelial cells, and reverse an allergic Th2 inflammatory transcriptome signature.²⁴ Given the weight of evidence documenting that PPIs reduce esophageal eosinophilia, A working Group on PPI-REE (AGREE) is putting forth an updated diagnostic algorithm for EoE that includes the removal of the PPI trial requirement and suggests that PPIs are better classified as a treatment rather than as a diagnostic criterion for EoE.¹⁹

EoE Therapy: Diet vs. Steroids? The advantages of using diet therapy over steroid therapy to treat EoE (particularly over the long-term) were reviewed. Diet therapies achieve histologic remission, consistently resolve symptoms, and may mitigate long-term esophageal complications by reversing epithelial hyperplasia and sub-epithelial fibrosis.^{18, 25-27} Elimination diet therapies can be a practical treatment for patients of all ages, and with the assistance of dietitians, diet therapies may improve the nutritional quality of patients' diets.²⁸ In recent years, elimination diets have become easier to follow, as food manufacturers have improved the palatability of foods used as substitutes for eliminated foods. Though therapies for EoE should be individualized and based on the patients' lifestyle and clinical needs, diet therapy has become an increasingly feasible treatment option for many patients.

EoE Therapy: Steroids vs. Diet? The advantages of using steroid therapy over diet for patients with EoE was reviewed (Table 1). Important points favoring steroid therapy include that the use of topical corticosteroids is effective at achieving histologic, endoscopic, and symptomatic

endpoints while preventing complications such as fibrosis and food impactions.²⁹⁻³¹ This treatment offers good tolerability with minimal impact to quality of life and without the use of multiple endoscopies. Topical corticosteroids have a good side effect profile, and complications are rare. Overall, the right choice on initial therapy is very individualized and patient driven, being based on consideration of the goals of care and what fits best with the individual's lifestyle and needs.

Nutritional Implications of EoE. Children with EoE may be at increased nutritional risk. A number of studies have reported poor growth at diagnosis in the pediatric population with EoE.³² ³³ Although there appears to be greater risk of stunting and being underweight in children with IgE-mediated food allergy on cow's milk or multiple food elimination diets, studies in children with EoE on elimination diets do not indicate growth consequences when the patient is under the care of a dietitian; receiving adequate energy, protein, and micronutrients; and/or using a supplemental formula to support the diet. Feeding difficulties in EoE have also been reported, and data exist that many children with EoE have maladaptive eating behaviors on the basis of a validated behavioral feeding assessment scale. Tools have been developed through an AAAAI workgroup report to assist practitioners in minimizing the nutritional impact of EoE and the associated dietary therapies used in disease management.³⁴

IgG vs. IgE and Disease Pathogenesis. The importance of IgE versus IgG4 in the pathogenesis of EoE was discussed. On one side, it was concluded that IgE may not have a major role in EoE for several reasons including: 1) symptoms are typically not temporally related to food triggers; 2) skin prick tests and serum IgE levels to foods are only weakly predictive of food triggers^{35, 36};

and 3) allergy test-based elimination diets (directed by skin prick tests, serum food-IgE levels, and IgE measurement of allergenic molecules by component-resolved diagnostics) are not that effective in inducing EoE remission.^{37, 38} Furthermore, omalizumab, an antibody targeted against IgE, was not effective in inducing EoE remission in a double-blind, placebo-controlled clinical trial.³⁹ IgG4 was thought to potentially have a role in the pathogenesis of EoE, though the current evidence for this is still preliminary. Serum, plasma, and esophageal tissue IgG4 levels to common food triggers were shown to be elevated in patients with EoE, though the elevation was not predictive of food triggers in these patients.^{40, 41} It was therefore concluded that higher levels of IgG4 than IgE are produced in EoE and that evidence to support IgG4 involvement directly in disease pathogenesis is needed. There is evidence of a Th2 phenotype in the blood and biopsy, indicating that T cell function may play a key role in disease pathogenesis.⁴²

The role of T cells in EoE pathogenesis. Patients with active EoE have local Th2 inflammation characterized by high levels of IL-13, IL-4, IL-5, thymic stromal lymphopoietin (TSLP), chemokines that attract eosinophils (e.g., eotaxins), lymphocytes, mast cells, basophils, and invariant natural killer cells (iNKT).^{43 44} Th2 polarization may be favored by genetic background in patients with EoE with higher production of epithelial factors such as TSLP, thereby promoting the differentiation of naïve CD4⁺ T cells into type 2 T helper (Th2) cells.⁴⁵ Accumulating evidence suggests that both innate (i.e., iNKTs) and conventional T cells are able to recognize and mount a Th2 response against food antigens in patients with EoE. Mouse models have demonstrated that T, but not B, cells are essential for EoE development.⁴⁶ iNKTs are increased at the site of inflammation and have a Th2 phenotype in patients with EoE.^{47, 48} Milk-derived lipid antigens are able to specifically activate iNKT cells and induce a Th2

response in patients with EoE.^{47, 49} In addition, patients with active EoE disease triggered by milk consumption have a significant increase of activated peripheral blood CD4+ T cells expressing Th2 cytokines compared to that of healthy controls or patients with inactive EoE.⁴² This CD4+ T cell population is capable of in vitro, milk-specific antigen responses.^{42, 50} These data confirm that both innate and adaptive T cells could have a central role in antigen recognition and initiation of Th2 inflammation.

Mast Cell Involvement. Mast cells are increased in active EoE, and their counts correlate with eosinophil levels and decrease with treatment in a majority of patients with EoE.⁵¹ Mast cells may have a role in symptoms via esophageal nerve activation and smooth muscle contraction, and the mast cell transcriptome correlates with dysphagia scores. Mast cells have a potential role in fibrosis and esophageal remodeling, and their esophageal density correlates with endoscopic furrows.

Less Invasive Testing. Less invasive testing for evaluating the esophagus is a rapidly growing area of clinical medicine and inquiry. Such testing includes methods that replace endoscopy or complement endoscopy with or without sedation. Most of these modalities are generally not currently available, except for endoscopic functional lumen imaging probe (EndoFLIP), unsedated transnasal endoscopy (TNE), and the EoE Diagnostic Panel (EDP). Other technologies will likely becoming more clinically available soon, such as the esophageal string test (EST), mucosal impedance, and cytosponge that are currently only available in research settings. These technologies have the opportunity to enable improved monitoring of the esophagus with lower cost but have tradeoffs compared to a more complete, biopsy-centric mucosal exam with sedated

endoscopy. Other complementary technologies may offer additional information regarding esophageal compliance or more rapid assessment of mucosa as compared to mucosal pathology, but the usefulness of such testing is debated.

Patient Advocacy. The positions of patient advocacy groups were presented. In particular, the many challenges of rare diseases were discussed, from obtaining a correct diagnosis to limited treatment options to finding a knowledgeable physician.⁵² Patients with EGIDs have limited treatment options for a life-long disease that significantly impacts quality of life. Patient advocacy groups like the American Partnership for Eosinophilic Disorders (APFED) can help physicians by assisting patients in finding support, lay friendly educational materials, patient conferences, and practical tools for everything needed to live life to the fullest.

Pilot Studies with Potential to Impact EGIDs. The CEGIR Pilot Study Program examines novel areas that have potential to create or change diagnostic and therapeutic paradigms concerning EoE, EG, and EC.¹⁹ Currently, four pilot studies have been funded and are active: 1) a microbiome initiative examining the gastrointestinal mucosal and fecal bacterial genomes in EoE, EG, and EC; 2) a prospective clinical trial of losartan in EoE; 3) a prospective trial of elemental diet in adults with EG; and 4) a prospective study examining the utility of TNE in children with EoE. Characterization of dysbiosis of the intestinal tract should provide fundamental insights into the pathogenesis of EGIDs. The losartan and elemental diet trials are the first prospective evaluations of such treatments in the indicated diseases. Finally, the evaluation of TNE may reduce the necessity of anesthesia during endoscopy during food reintroduction, a major limitation of the elimination diet approach in EoE.

Endotypes in Eosinophilic Esophagitis: Three EoE endotypes have been indentified based on probing esophageal biopsies from pediatric and adult EoE subjects across sites associated with CEGIR using the EoE Diagnostic Panel (EDP), a set of 95 informative transcripts.⁵³ Of histological features, basal zone hyperplasia (BZH) correlated relatively strongly with the EDP and of different endoscopic features, furrows correlated relatively strongly with the EDP. The EDP identified three clusters associated with distinct endotypes (termed EoEe1-3) despite similar eosinophil levels. EoEe1 was strongly associated with a normal-appearing esophagus and showed relatively mild histologic, endoscopic and molecular changes. EoEe2 demonstrated an inflammatory and steroid-refractory phenotype and showed the highest expression of cytokines and steroid-responding genes. EoEe3 was strongly associated with a narrow-caliber esophagus and showed the highest degree of endoscopic and histologic severity and the lowest expression of epithelial differentiation genes. These endotypes have potential to allow tailoring of EoE specific therapy, as well as prognosis predictions.

Predicting the future in EGIDs: The potential needs for patients, researchers and physicians were discussed for the immediate future and next 10 years (Table 2). The major developments will be availability of FDA approved medications in EoE and less invasive biomarkers for diagnosis. In the more distance future, personalized medicine based on genetics and genomics on esophageal biopsy samples, is likely to advance patient care and understanding.

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Table 1: Pro and Cons of Diet vs Steroids

Dietary Therapy		Swallowed Steroids	
Pro	Con	Pro	Con
“natural”	Lower quality of life to adjust to dietary restrictions and poor palatability in the case of elemental diet	Ease of use	Side Effect-esophageal candidiasis (5-10%)
Removing upstream trigger of disease	Grocery cost of restricted diet	Not Approved by FDA	Theoretical Adrenal and growth suppression
Highest response rate with elemental diet	Multiple endoscopies	Improved Quality of Life	Cost of unapproved medication
Reverse fibrosis		Reverse fibrosis in children	
Reduce symptoms		Reduce symptoms	
Decrease eosinophil count and improve histological pathology		Decrease eosinophil count and improve histological pathology	

Table 2: Future Needs in Eosinophilic Gastrointestinal Disease

Need	Near Future	Far Future
Drug Approval	Topical esophageal corticosteroid (adults)	Biologics for disease modification- anti-IL-13; anti-IL-4Ra; eosinophili depleting antibodies and drugs. Small molecule inhibitors for mast cell, eosinophil, T cell, and/or epithelial cell function and/or modification
Personalized medicine	Endotype-Based Therapy based on esophageal transcriptome profiling (e.g. EoE Diagnostic Panel) PPI responsive patients	Genetic SNP based therapy
Inflammation-dependent and independent remodeling therapy	Biologics, e.g. anti-IL-13 in adults	Inflammation independent anti-fibrotic therapy
Understanding long term complications and long-term response to therapy	Multicenter, across the U.S.	Genotype-Phenotype variability Natural history in large cohorts

		of children
Less invasive or non-invasive biomarkers	Esophageal string test Transnasal endoscopy Sponge test	Peripheral blood markers/panels
Improved Diet Therapy	One food elimination (e.g. milk elimination diets)	Induction of food tolerance

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