Eosinophilic Esophagitis: From Soup to Nuts

Emily C. McGowan, MD PhD & Bryan G. Sauer, MD MSc
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From Soup . . . . . . to Nuts

EoE  PPI-REE  SFED  GERD
Disclosures

Emily McGowan
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Bryan Sauer
- None

There are currently no FDA-approved therapies available for Eosinophilic Esophagitis (EoE)

Objectives

- Describe the clinical presentation of EoE in adults
- Review the history and epidemiology of this recently described condition
- Discuss the known pathophysiology and the role of allergy in EoE
- Review current guidelines for diagnosis and options for management
Please welcome our patient . . .

Eosinophilic Esophagitis
First Described in 1977

EOSINOPHILIC GASTROENTERITIS WITH ESOPHAGEAL INVOLVEMENT

JOHN W. DORNIS, M.D., DANIEL G. SHEHAM, M.B., M.Sc., AND JOSÉ BEHR, M.D.

Department of Internal Medicine and Pathology, Yale University, New Haven, Connecticut, and The West Haven Veterans Administration Hospital, West Haven, Connecticut

A patient with a lifelong history of asthma and hay fever was investigated because of symptoms of esophageal spasm. Esophageal biopsies revealed elongated papillae and basal zone hyperplasia of the epithelial layer with eosinophilic infiltration of the lamina propria and muscularis mucosae. There was no evidence of reflux. Small bowel biopsies revealed a flat mucosal pattern with absent or blunted villi, tall columnar surface epithelium, and eosinophilic infiltration of the lamina propria. He did not respond to a gluten-free diet. This patient is thought to have eosinophilic gastroenteritis with esophageal involvement, the first such case reported.

Timeline of Allergic Disease

~400 BC: Asthma first defined by Hippocrates
1 AD: Celiac Disease first described
1662: First report of food allergy in the medical literature
1819: Allergic Rhinitis first defined
1977: EoE first described (case report)

University of Virginia Health System
History of EoE

1977: EoE first described (case report)
1980s: Papers linked eosinophilia with GERD
1993 & 1994: 2 case series defined EoE as a distinct condition
1995: Food was found to be causative factor
1998: Topical steroids first used
2000: 2003-2007 Retrospective studies
2008: ICD-9 Code first implemented
2010: 2013: Revised consensus guidelines
2011: Revised consensus guidelines
2018: Revised consensus guidelines

EoE Publications by Decade

Number of publications

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Epidemiology

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

Prevalence Estimates

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

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

Dellon ES, Gastroenterology, 2018
Rothenberg ME et al, Gastroenterology 2015
Arias A et al, AP&T, 2016
Prasad GA et al, Am J Gastro, 2007
Hill DA et al, JACI-IP, 2017
Prevalence Estimates

McGowan EC, unpublished data

EoE Appears to be Increasing

Dellon ES, *Gastroenterology*, 2018
Evidence for a True Increase

Diagnosis Outpaces Biopsies  
EoE Not Missed in the Past

Why is EoE Increasing?

- Hygiene hypothesis?
- Changing aeroallergen exposure?
- Changes in food allergens?
- H. pylori eradication?
- Increased use of PPIs?
- Early life exposures?

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

Dellon ES et al, AP&T, 2015  
DeBrosse CW et al, JACI, 2010
Natural History

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

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

Progression to Fibrosis

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

Dellon ES, Gastroenterology, 2018
Pathophysiology

Remind me . . . eosinophil?

- Granulocyte that develops in the BM and then circulates to the tissue
- Increases during helminth infections and in allergic disease
- Proliferation and survival driven by IL-5
- Can release cationic proteins, lipids, and chemokines upon stimulation
EoE is an Allergic Disease

- ~75% of patients with EoE are atopic
  - Atopic Dermatitis: 40-60%
  - Allergic Rhinitis: 40-74%
  - Asthma: 40-70%
  - Food Allergy: 15-43%
- Disease activity in the esophagus can often be reversed with empiric food elimination diets or elemental formula
- EoE is associated with a "Th2" profile
  - IL-4, IL-5, IL-13
  - More evidence points away from IgE

González-Cervera J et al, Annals, 2017
O’Shea KM, Gastroenterology, 2017

EoE has a Genetic Basis

- Twin studies:
  - Monozygotic twins: 58%
  - Dizygotic twins: 36%
  - Non-twin siblings: 2.4%
- GWAS and candidate gene studies:
  - TSLP, calpain 14 (CAPN14), LRRC32, STAT6
- “EoE Transcriptome”

Rothenberg ME et al, Gastroenterology 2015
Pathophysiology

Diagnosis (circa 2013)

- **A clinicopathologic disorder defined by the following criteria:**
  - Symptoms related to esophageal dysfunction
  - Eosinophil-predominant inflammation on esophageal biopsy (≥15 eos/hpf)
  - Mucosal eosinophilia is isolated to the esophagus and persists after a PPI trial (otherwise this was called PPI responsive esophageal eosinophilia PPI-REE)
  - Secondary causes of esophageal eosinophilia are excluded

Dellon ES *et al.* Am J Gastroenterol 2013
Diagnosis (2019)

- A clinicopathologic disorder defined by the following criteria:
  - Symptoms related to esophageal dysfunction
  - Eosinophil-predominant inflammation on esophageal biopsy ($\geq 15$ eos/hpf)
    - Mucosal eosinophilia is isolated to the esophagus and persists after a PPI trial
  - Secondary causes of esophageal eosinophilia are excluded

Dellon ES et al. Am J Gastroenterol 2013

No More PPI-REE?

1. Clinical, endoscopic, histologic, immunologic, and molecular similarities between EoE and PPI-REE
2. EoE and GERD are not mutually exclusive
3. Other mechanisms of PPIs can explain the response of eosinophilia
4. PPI-REE also responds to classic EoE treatments

Dellon ES et al. Gastroenterology 2018
Diagnosis

A clinicopathologic disorder defined by the following criteria:

- Symptoms related to esophageal dysfunction
- Eosinophil-predominant inflammation on esophageal biopsy (≥15 eos/hpf)
- Secondary causes of esophageal eosinophilia are excluded

Dellon ES et al. Gastroenterology 2018
Typical Symptoms in Children

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

Typical Symptoms in Teens/Adults

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

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

Dellon ES et al. Gastroenterology 2018
Endoscopic findings

- Esophageal rings (trachealization)
- White exudates or plaques
- Longitudinal lines/furrows
- Edema – mucosal pallor or decreased vascularity
- Diffuse esophageal narrowing
- Esophageal lacerations with endoscope passage

![Endoscopic images]

Patchy Inflammation

![Graphs showing endoscopic findings]

How many biopsies?

- Inflammation can be patchy
- Studies show more biopsies increases diagnostic yield
- General recommendations: 2-4 biopsies from at least TWO different locations
- Current Practice
  - 6 biopsies from distal esophagus, 6 biopsies from mid/prox esophagus


Histology

- AGA consensus: > 15 eos/hpf
- Definition in literature varies
- Multiple biopsies (>5) recommended

Dellon ES et al. Gastroenterology 2018
Diagnosis

A clinicopathologic disorder defined by the following criteria:

- Symptoms related to esophageal dysfunction
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Dellon ES et al. Gastroenterology 2018
Secondary Causes

- GERD
- Eosinophilic gastrointestinal disease
- Crohn’s disease
- Infections (parasitic, viral, fungal)
- Hypereosinophilic syndrome (HES)
- Achalasia
- Drug hypersensitivity
- Vasculitis
- Graft versus host disease
- Mendelian disorders (Marfan Syndrome type II, hyper-IgE syndrome, Netherton syndrome)

Treatment Options

1. Proton Pump Inhibitors (PPI)
2. Swallowed Steroids
3. Dietary Therapy
4. Periodic Esophageal Dilations
5. Biologics?
Treatment Options

1. Proton Pump Inhibitors (PPI)
2. Swallowed Steroids
3. Dietary Therapy
4. Periodic Esophageal Dilations
5. Biologics?
Proton Pump Inhibitor

- Leads to remission in 33 - 74% of patients
- Long-term efficacy is not well-established
  - ~78% of children remained in remission after 1 y
  - ~75% of adults remained in remission after 2 y
- Relatively safe and well-tolerated

Francis DL et al, Aliment Pharm Therapy, 2012

How often will eosinophilia respond to PPI?

431 adults: histological response 50%

Treatment Options

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

Swallowed Steroids

Pros
- Patients can eat what they want
- It’s very effective (60-90% remission)

Cons
- It’s a medication patients have to take every day
- There is a risk for steroid side effects and esophageal candidiasis (10-20%)
**Fluticasone**

- Spray MDI in mouth with lips sealed around device and swallow
- No eating, drinking or rinsing for 30 minutes
- Possible to use Fluticasone DPI preparation

**Budesonide**

- Thicken the liquid with:
  - Sucralose
  - Honey
  - Neocate Nutra
  - Applesauce
  - Lemonade Mix
- Dose:
  - Children → 1g/day
  - Adults → 2g/day
Treatment Options

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Food Elimination Diets

- Elemental Diet
- Allergy-testing directed
  - Skin-Testing Guided
  - Serum IgE-Guided
- Empiric Elimination Diets
  - 6 Food Elimination Diet (SFED)
  - 4 Food Elimination Diet (FFED)
  - 2 Food Elimination Diet (TFED)
  - Milk Only Elimination Diet
Food Elimination Diets

**Pros**
- The patient gets to the underlying source of inflammation
- Typically leads to long-term remission (with continued food avoidance)

**Cons**
- The patient has to avoid foods that are commonly consumed
- It takes multiple EGDs to identify the causative food
- It can be expensive to find alternative foods

Elemental Formula Diet

- Has been studied in both children and adults
- Histologic remission:
  - Children: 90.4%
  - Adults: 94.4%
- Associated with poor adherence and significant weight loss in adults
- Often requires placement of a G-tube in children

References:
- Kelly KJ, Gastroenterology, 1995
- Peterson KA et al. Am J Gastroenterol 2013
- Arias A, Gastroenterology, 2014
Allergy-Testing Directed Diets

- Has been studied in both children and adults
- Overall efficacy: 45.5%
  - Children: 47.9%
  - Adults: 32.2%
- Not recommended anymore to direct diet
- Still a role for allergy testing to assess:
  - Aeroallergen sensitization
  - Risk of IgE-mediated reactions

Molina-Infante J. JACI 2012

Empiric Elimination Diets

- Six Food Elimination Diet (SFED)
- Four Food Elimination Diet (FFED)
- Two Food Elimination Diet (TFED)
Six Food Elimination Diet

- Most common foods implicated
- Studied in both children and adults
- Overall efficacy: 72.1%
  - Children: 72.8%
  - Adults: 71.3%

Kagalwalla, Clin Gastro Hep, 2006
Gonsalves N et al. Gastroenterology, 2012
Lucendo et al, JACI, 2013

Four Food Elimination Diet

- **Dairy**: All mammalian milk
- **Wheat**: Gluten-containing foods
- **Legumes**: Soy, lentils, beans, peas, and peanuts
- **Egg**

Efficacy:
- Children: 65%
- Adults: 54%

Molina-Infante J et al. JACI 2014
Kagalwalla AF et al, Clin Gastro Hepatol, 2017
Two Food Elimination Diet

- Studied in children and adults
- Efficacy: 43%
- Reduced the number of EGDs by 20%

Molina-Infante J. JACI 2018

Food Elimination Diets

FIG 3. Per-protocol remission rates on a TFGED (58 patients) and after a step-up intervention with an FFGED (10 patients) and an SFGED (7 patients).

Molina-Infante J. JACI 2018
Treatment Options

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

Pathophysiology

Davis BP, Clin Rev Allergy and Immunol, 2018
Biologics

Mepolizumab (anti-IL-5)

Biologics

QAX576 (anti-IL-13)

Davis BP, Clin Rev Allergy and Immunol, 2018
Biologics

Dupilumab (anti-IL-4Rα)

Potential targets

Davis BP, Clin Rev Allergy and Immunol, 2018
How to decide on treatment strategies?

- Multidisciplinary team
  - GI, allergy, nutrition
  - Patient and patient family

- Adult EoE Clinic
  - Started in October 2016 at UVa

Take Home Points

- Think of EoE when seeing an atopic patient with feeding aversion, nausea/regurgitation, or dysphagia
- Have a low threshold to refer to GI for EGD/biopsies
- Our current testing modalities have limitations in diagnosing food triggers in EOE
- Treatment is individualized with options including PPI therapy, swallowed steroids, and dietary modifications
Thank You!

Questions?
References


References (cont)

References (cont)


References (cont)