Eosinophilic Esophagitis- Recognition, Management, and Misperceptions

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Objectives

• Recognize the signs and symptoms of eosinophilic esophagitis (EoE) in different age groups
• Appreciate the change in our understanding of the pathophysiology of EoE
• Understand how EoE is diagnosed
• Discuss the treatment options for EoE

• No financial or other disclosures
• 7yo male with difficulty swallowing x 1 year
  – Occurs when eating
  – Solids worse than liquids
  – Occasional heartburn
  – No choke/gag/cough
  – “Feels food go down”
Differential Diagnosis - Dysphagia

- Esophagitis
  - GERD
  - Eosinophilic Esophagitis (EoE)
  - Infectious
- Anatomic/vascular anomaly
- Traumatic injury
- Psychosomatic

- Crohn’s Disease
- Motility (i.e. achalasia)
- Mediastinal mass
- Neurologic
- Connective tissue disease
Additional History…

- Washes food down with water
- Slow eater
- Fine in between episodes
- Weight gain slowed
- IgE mediated food allergy to peanuts
- Father with chronic dysphagia, food impaction age 20s; “has not gotten it checked”
What is Eosinophilic Esophagitis (EoE)?

- Chronic inflammation of esophagus
  - Eosinophil dominant

- Immune-mediated

- Food (?aeroallergen) trigger

So what?
Why EoE Matters

- #2 cause esophagitis

- Leading cause of dysphagia and food impaction in kids and adults

- Complications

- Incidence rising
Symptoms Vary by Age

- Abdominal pain, vomiting, dysphagia

- Infants/Toddlers
  - Feeding difficulties (gag/choke/refusal), vomiting

- Children
  - Vomiting/GER, nausea, abdominal pain, chest pain, poor growth

- Adolescents/adults
  - Dysphagia, food impaction, chest pain
Epidemiology

- Incidence 1/10,000\(^1\)
- Prevalence 5-10/10,000

- Young men (3:1)\(^2\)
- Age 30-50yo
- High rate atopy
  - 2/3- allergic rhinitis, asthma, eczema
  - IgE mediated food allergy common (15-40%)
  - Up to 75% have personal or family history\(^3\)

Why the Rise?

- Environmental
  - Hygiene hypothesis
  - Dietary changes (antioxidants, fats, Vitamin D)
  - Food processing
  - Delayed oral exposure to foods
- Early antibiotics
- C-section
- Prematurity
- Microbiome
- Infectious- HSV, Mycoplasma; H. pylori (inverse)
- Oral/sublingual immunotherapy
- PPI, low Vit D
Evaluation & Diagnosis
• **Physical exam— no diagnostic findings**
  – Allergic shiners
  – Rhinitis
  – Reactive airways
  – Atopic dermatitis

• **Laboratory— no diagnostic tests**
  – Mild peripheral eosinophilia in <50% with EoE\(^1\)
  – Allergy testing (skin prick, IgE)
    • No direct correlation with non-IgE mediated disease

• Other questions to ask:
  – Onset with introduction of solids?
  – Slow eater?
  – Drink to wash down food?
  – Particular food avoidance?
  – Excessive chewing?
  – Other atopy-patient, family?
  – Growth failure?
- Up to 30% who have histologic EoE have endoscopically normal mucosa

• Increased eos/HPF, microabscesses, superficial layering, basal zone hyperplasia

Concentric rings in esophagus
Diagnostic Criteria Has Changed

• 2007\(^1\)
  – $\geq 15$ eos/HPF, PLUS
  – Characteristic symptoms which do not respond to high dose PPI therapy, OR normal pH monitoring\(^1\)

• 2011-Proton Pump Inhibitor-responsive Esophageal Eosinophilia (PPI-REE)\(^2\)
  – $\geq 15$ eos/HPF, PLUS
  – Symptoms of esophageal dysfunction, PLUS
  – Improvement/resolution of symptoms and eosinophilia after high dose PPI

Assumptions

1. GERD and EoE distinct

2. GERD is the only esophageal condition that responds to PPI¹

¹Dellon et al. Gastroenterology Vol 155 2018
New Understanding

• AGREE (A Working Group on PPI-REE)¹
• GERD and EoE may overlap

1. EoE → GERD? (dysmotility)
   GERD → EoE? (impaired mucosal barrier)
2. EoE and PPI-REE similar histologically
3. RNA expression profiles similar
4. Atopy present in EoE and PPI-REE
5. PPI-REE responds to EoE treatment (topical steroids, dietary elimination)

PPIs-More Than Gastric Acid Inhibition

Non-acid related mechanisms

– Antioxidant
– Blocks secretion of eosinophil trafficking molecule (eotaxin-3)
– Proton pumps in inflammatory cells and non-gastric cells
– Patients with normal pH probe can respond to PPI therapy
Management
Goals

- Symptom control
- Histologic normalization
- Reversal of remodeling
- Avoidance of complications
Treatment Options

• 2011
  – Elimination Diet
  – Swallowed Topical Steroid

• 2019
  – PPI
  – Elimination Diet
  – Swallowed Topical Steroid
Dietary Therapy
Classification of Food Allergy

• IgE mediated
  – Acute (anaphylaxis, oral swelling)

• Cell mediated (Delayed/chronic)
  – Delayed/chronic (FPIES, food protein proctitis)

• Mixed IgE/cell mediated
  – Delayed/chronic (eosinophilic GI disease, eczema)
  – Serum IgE and Skin Prick Testing → not helpful in EoE!
Dietary Options

1. Elemental
2. Empiric 6, 4, 2, 1 elimination
3. Directed elimination
Determining dietary modification

**IgE Mediated**
- Cow’s Milk
- Egg
- Peanut
- Tree nuts
- Fish
- Shellfish
- Wheat, soy
- Sesame

**EoE**
- Cow’s milk
  - 40-90%
  - 50% only trigger\(^1\)
- Wheat
- Egg
- Soy

\(^1\)Kagalwalla AF et al. Clinc Gastroenterol Hepatol 2017.
Elimination Diets for EoE

- **Elemental**
  - 90% remission\(^1\)
- **6 Food: Dairy, wheat, soy, egg, nuts, fish/shellfish**
  - 50-75% remission\(^2\)
- **4 Food: Dairy, gluten, egg, legumes**
  - 50-65% remission\(^2\)
- **2 Food: Dairy, gluten**
  - 43% remission\(^3\)

\(^1\)Aria A et al. Gastro 2014.
\(^2\)Molina Infante J et al. J Allergy Clin Immunol 2018
\(^3\)Molina-Infante J et al. [Expert Rev Gastroenterol Hepatol], 2017
Dietary Options

• **Directed Elimination:**
  – 12 single arm studies → 50% remission$^1$
    • Testing techniques varied
  – Not effective

$^1$Hirano I et al. AGA Clinical Guidelines 2019.
Pharmacotherapy
PPI

• 1-2 mg/kg/day divided BID
• Max dose- Lansoprazole 30mg BID, Omeprazole 40mg BID
• 23 observational studies→40% histologic improvement¹
  – Heterogeneous studies

¹Hirano I et al. AGA Clinical Guidelines 2019.
• **Swallowed topical steroids**
  - Fluticasone
  - Budesonide slurry
  - 8 double-blind placebo controlled studies
    - 66% remission vs. <15% placebo¹

• **TRY TO AVOID:** Systemic steroids
• **NOT:** Mast cell stabilizers (Cromolyn), leukotriene antagonists (Montelukast), biologics (Anti-TNFα, Anti-IL5, Anti-IL13)

¹Hirano I et al. AGA Clinical Guidelines 2019
Swallowed Topical Steroids

- **Fluticasone**
  - 1-4yo: 44 mcg, two sprays twice daily
  - 5-10yo: 110 mcg, two sprays twice daily
  - ≥11yo: 220 mcg, two sprays twice daily

- **Budesonide**
  - < 10yo: 1 mg daily
  - > 10yo: 2 mg daily
Limitations in Current Data

• No prospective, double-blind, randomized trial to compare PPI to diet or steroid
  – Small studies, retrospective
  – Inconsistent study design
    • PPI duration, dose
    • PPI responder vs. non-responder
  – Lack consistent definition re: clinical or histologic response
Risks/benefits: PPI vs. Diet vs. Topical Steroid

- **PPI**
  - Long term safety concerns

- **Diet**
  - QOL
  - Developmental feeding & social skills
  - Cost
  - Possible NG/Gtube

- **Topical steroid**
  - Local infection
  - Adrenal suppression
  - Growth?
Natural History

- Esophageal subepithelial remodeling
- Increased angiogenesis
- Vascular activation
  - conduits for inflammatory cell trafficking
  - collagen deposition, accumulation of matrix proteins
  - eosinophil accumulation
EoE Is Chronic, Progressive

- 2003- Straumann A et al
- 30 adults, 7 year follow-up
  - No medical therapy
  - Dysphagia
    - 40% better, 40% stable, 25% worse
    - Subepithelial fibrosis- worse 86%

- Limitations:
  - 1/3 s/p dilation
  - 50% altered eating habits
Do Not Delay Diagnosis

• Symptom as outcome: *lack of significant progression*
  • Dysphagia children → adult: 30-50%
  • Patients adapt
• Histology as outcome: *significant progression of fibrosis*

#1 risk factor fibrostenotic disease = *delay in diagnosis*
Challenges

• Natural history of EoE still not fully understood
  – Variable symptoms—different phenotypes?
  – Outcomes in asymptomatic patients
  – Consistent symptom, histologic endpoints

• Distinguishing EoE from GERD

• Non-invasive methods for assessing disease
  – Less invasive diagnostic modalities
  – Histologic biomarkers
  – Genetic markers
• **Treatment**
  – Loss of therapeutic efficacy
  – Role of rescue therapy for “flares”
  – Biologic therapy
  – Need clinical trials comparing therapies
Take Home

- Symptoms differ by age
- Symptoms do not correlate with histology
- Food allergy testing not reliable
- Need upper endoscopy with biopsies to diagnose
- EoE and PPI-REE same entities
  - PPI, dietary elimination, and topical steroids
- Avoid delay in diagnosis
EoE Referrals

- **Pediatric Specialists of Virginia**
  Fairfax, VA
  703.876.2788
  – Jaime Wolfe, MD & Darlene Mansoor, MD
  – Otto Louis-Jacques, MD

- **Children’s National Health System**
  Friendship Heights
  202.476.3032
  – Seema Khan, MD & Hemant Sharma, MD