Overview of Eosinophilic Esophagitis

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Conflict of Interest Disclosure
I have no conflicts and nothing to disclose.

Learning Objectives
• Define Eosinophilic Esophagitis (EoE)
• Review the history of the development of EoE
• Describe the signs and symptoms of EoE
• Discuss evaluation and treatments for EoE
Eosinophil basics

- A type of granulocyte
- Play a role in the body’s defense against helminthic parasites and allergic disease
- Located in various places throughout the body
  - Gastrointestinal tract
  - Thymus
  - Mammary gland
  - Uterus

Eosinophils in the GI Tract

GI Diseases associated with Eosinophilia

- EGIDs (Eosinophilic GI Diseases)
  - Eosinophilic gastritis
  - Eosinophilic enteritis
  - Eosinophilic gastroenteritis
  - Eosinophilic colitis
  - Includes Food Protein Induced Enterocolitis (FPIES)
- Celiac disease
- Inflammatory bowel disease
- Achalasia
- Graft versus host disease
- Infection
Dr. Kelly’s seminal paper

- In 1995 he reported 10 patients with severe reflux (GER)
  - All had EGDs and were noted to have esophageal eosinophilia
  - Patients were taking a proton pump inhibitor (PPI) or had a Nissen fundoplication
- Patients consumed only an amino acid-based (elemental) formula for a period of 6 weeks

What happened to Dr. Kelly’s patients?

- On the elemental formula
  - 8 patients had no symptoms
  - 2 patients’ symptoms improved
  - Esophageal biopsies improved as well
- Once off of the elemental diet symptoms returned
- Conclusions
  - EoE is an allergic process
  - EoE improves with certain food changes

History of Eosinophilic Esophagitis development

- Rare cases of patients with eosinophils in the esophagus were described in the 1970s
  - Related the eosinophils to GER
- Endoscopic findings noted in 1983 (Riley Childrens)
- Given the distinct diagnosis in 1995
  - Kelly et al.
- Guidelines created in 2007 and revised in 2011
  - Adult and pediatric gastroenterology and allergy
- American Gastroenterology Association guidelines in 2018

Epidemiology of EoE

• The number of cases of EoE is greatly increasing in the past several years

• Incidence 3.7/100,000 a year
• Prevalence in US 57/100,000
  — Comparison to IBD 400/100,000

• Reported on all continents
  — Prevalence highest in Western Europe, Australia and United States


Why the rise in EoE?

• Hygiene hypothesis
  — Seen with other atopic diseases
• Antibiotics in infancy
• Allergen exposure to infants or mothers
• Change in microbiome
• Gastroesophageal reflux disease
• Previous use of Proton pump inhibitor (PPI)
• Environmental toxins or additives

What is EoE?

• Based on 2007 guidelines and updates:

1. Clinico-pathological condition that is immune or antigen driven
2. Symptoms of esophageal dysfunction
3. Esophageal biopsies ≥15 eosinophils/high powered field (hpf) on at least one biopsy

Who are the patients with EoE?

Characteristics of EoE patients

• Males
  – Related to 17β estradiol
• Caucasian predominance
• Genetics
  • Increased incidence in siblings and 1st degree relatives
  • Twin studies show 2.4% risk in siblings
Characteristics of EoE patients

- **Associated co-morbidities**
  - Atopic diseases
    - Asthma
    - Food allergies
    - Eczema
  - Autoimmune diseases
    - Celiac disease
      - Seen only in pediatrics thus far
    - IBD
  - Connective tissue disorders
  - Neuropsychiatric developmental disorder
    - Autism

- **Environmental factors**
  - Antibiotic use in infancy
  - Penicillin allergy
  - Non-smokers

Pathophysiology of EoE

- Immune system activation by intraluminal allergen exposure
- Mucosal production of eosinophilic chemoattractants
- Release of inflammatory mediators
- Esophageal dysfunction
Clinical presentation of EoE

- Feeding difficulties
  - Poor weight gain
  - Choking
  - Vomiting
- Pain
  - Chest or abdominal
- Reflux symptoms
- Difficulty with swallowing (dysphagia)
- Food getting stuck (food impaction)

Symptoms of EoE according to age

Common patient scenarios

1. 2 yo female with long standing history of regurgitation, poor weight gain and eczema.
2. 34 yo male who has been to the ER three times for a food impaction after eating steak. The food impactions have resolved without medical intervention.
3. 15 yo male with history of celiac disease who now complains of several months of feeling like food is getting stuck when eating. He is now on an all liquid diet (formula).
How to evaluate for EoE

- Proceed with EGD for esophageal biopsy
- May include Upper GI imaging prior to EGD
  - Helps to evaluate for esophageal stricture or narrowing
- Stop all proton pump inhibitor therapy
  - New recommendation in the past 6 months

Imaging findings in EoE

Endoscopic findings of EoE

Furrows
Endoscopic findings of EoE

• EoE Endoscopic Reference Score (EREF5)
  – Standardized classification of endoscopic findings
  – Components
    • Edema, Rings, Exudates, Furrows and Strictures
  – Found that rings, furrows, exudates and edema were suggestive of EoE
  – Important to utilize because they may reflect more disease activity beyond the eosinophils

Histology of EoE

Normal esophagus

EoE

Hirano
Gut.
Where to go from here?

EoE treatment

- What are the goals of treatment?
  - Symptom resolution
    - Symptoms do not correlate well with endoscopic and histologic findings
  - Histological resolution
    - What is the acceptable number of eosinophils for resolution?
      - Less than 15/LF or zero?
    - Prevention of strictures and food impaction

EoE treatment

- Medications (Drugs)
  - PPIs
  - Topical corticosteroids
    - Fluticasone
    - Budesonide
  - Oral steroids
- Dietary therapy
- Esophageal dilation
PPI therapy for EoE

- 2018 –AGREE conference
  - Removal of PPI trial prior to EGD to evaluate for EoE
  - Symptomatic esophageal eosinophilia is now synonymous with EoE
- Histologic response rate
  - 50% in adults and 54% in pediatrics
- Exact mechanism of action is unknown
- Unknown if the response is sustained
- No studies that compare primary therapy of PPI to diet or steroids


Corticosteroids

- Oral steroids
- Topical corticosteroids
  - None are FDA approved for EoE therapy
    - Fluticasone
    - Budesonide


Oral corticosteroids

- Reserved for only severe patients
- Short term use only
- Relapse after steroids were stopped
- Side effects are common
  - Growth problems
  - Elevated blood sugar
  - Weight gain
Fluticasone proprionate

- Initial study in 1998 in 4 children
- Swallow medication
- Dosing
  - Children 88-440 µg twice a day
  - Adolescents and adults 440-880 µg twice a day
- Side effects
  - Oral candidiasis
  - Mild growth restriction
  - Adrenal suppression

Liquid budesonide

- First prescribed in 2005 for children who were unable to swallow fluticasone
- Mixed with sucralose, honey, elemental formula and swallowed
- Similar side effect profile as with fluticasone
  - Candidiasis
  - Elevated blood sugar
- Studies have shown both symptomatic and histologic improvement compared to placebo

Topical corticosteroids

- Response
  - 50-80% efficacy
- Adverse effects
  - Concern of candidiasis
  - Growth restriction
  - Adrenal suppression
    - Unlikely due to hepatic metabolism via cytochrome p450 to inactive metabolites
    - May consider stress dose steroids during periods of stress (illness, endoscopy)
- Initial dosing is twice a day; may decrease to daily
Dietary therapy

- Three approaches
  - Amino acid-based formula
  - Elemental diet
  - Empiric elimination diet
    - Six-food elimination diet
    - Four-food elimination diet
    - Cow's milk elimination diet
    - Targeted elimination diet
      - Based on allergy testing

Amino acid-based formula

- 96% efficacy when used for sole nutrition
- Advantages
  - Very effective
  - No need for medications
- Disadvantages
  - Not palatable
  - Difficult to maintain for a long time
  - May require NGT or Gastrostomy tube (G tube) for administration
  - May lead to oral aversion or interfere with development of oral skills
  - Alters quality of life significantly
  - Expensive

6 FED (“6” Food Elimination Diet)

- Cow’s Milk, soy, wheat, egg, peanut, tree nut and fish/shellfish
- 70% efficacy
- Advantages
  - No testing is needed
  - Not as restrictive as elemental diet
- Disadvantages
  - Requires multiple endoscopies
  - May not identify the causative food
  - May not be nutritionally complete
    - Require nutritionist input
    - Alter patient’s quality of life
Empiric dietary therapy

• Foods identified to be allergenic in EoE patients

Four food elimination diet

• Cow’s milk, soy, egg and wheat
  — Histological remission in pediatrics 73%
• Fish and shellfish, peanuts and tree nuts are not common trigger foods in EoE patients

Cow’s milk elimination diet

• 30-66% effective
• Advantages
  — Fewer endoscopies needed than with 6 FED
  — Nutritionally complete
  — Easier to follow than 6 FED
• Disadvantages
  — Affects patient’s quality of life
• Monitor Vitamin D status
Diet therapy for EoE

• Typically used in conjunction with PPI therapy
• In general:
  – Low risk foods: fruits and vegetables
  – Low-medium risk foods: tree nuts and peanuts, legumes, potato, rice
  – High risk foods: cow’s milk, meats, grains, soy, egg and corn
• EGD performed after each food is reintroduced into the patient’s diet
  – Need at least 4 weeks between each therapy change

What about food allergy testing in EoE?

• EoE is due to a food allergen so why not?
• Food allergy testing is based on IgE-mediated or T cell-mediated response
  – IgE-mediated responses
    • RAST serum testing, Skin prick testing
  – T cell-mediated response
    • Skin patch testing
• EoE is a combination of both responses so food allergy testing is not helpful for guiding diet therapy
• Can have false positives in general as well

**Food allergy testing in EoE**

<table>
<thead>
<tr>
<th>Food</th>
<th>sEoE</th>
<th>sAll</th>
<th>sEoE+sAll</th>
<th>sEoE+sMilk</th>
<th>sEoE+sNuts</th>
<th>sEoE+sSoy</th>
<th>sEoE+sWheat</th>
<th>sEoE+sPeanuts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>28.8%</td>
<td>55.1%</td>
<td>60.9%</td>
<td>60.9%</td>
<td>60.9%</td>
<td>60.9%</td>
<td>60.9%</td>
<td>60.9%</td>
</tr>
<tr>
<td>Egg</td>
<td>19</td>
<td>45.1%</td>
<td>46.0%</td>
<td>46.0%</td>
<td>46.0%</td>
<td>46.0%</td>
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<tr>
<td>Fish</td>
<td>34</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
</tr>
<tr>
<td>Nut</td>
<td>9</td>
<td>54.5%</td>
<td>54.5%</td>
<td>54.5%</td>
<td>54.5%</td>
<td>54.5%</td>
<td>54.5%</td>
<td>54.5%</td>
</tr>
<tr>
<td>Soy</td>
<td>26</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
</tr>
<tr>
<td>Wheat</td>
<td>36</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
<td>55.1%</td>
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</tr>
</tbody>
</table>

**EoE Consensus guidelines for dietary therapy**

- Dietary therapy should be considered and discussed in all EoE patients
- Dietary therapy may lead to complete or near complete resolution of both clinical and histological abnormalities
- Dietary therapy may reverse esophageal fibrosis
- Consultation with dietician is recommended to ensure proper nutrition

**EoE Complications**

- Esophageal stricture
  - 60% develop strictures after 10 years of disease
  - Food impaction
- Narrow-caliber esophagus
- Esophageal perforation
- Impaired development of oral skills

No reports of hypereosinophilic syndrome or malignancy
**Esophageal Dilation**

- Can lead to long-lasting symptomatic improvement in patients with esophageal strictures
- In children, recommended only in severe esophageal narrowing despite other forms of treatment
- May need repeat dilations over time

**Clinical course of EoE**

- Natural course of EoE is unclear
  - EoE is chronic and likely progressive, leading to irreversible structural damage of the esophagus
    - Complications
      - Esophageal fibrosis and strictures
      - Symptom duration before diagnosis is the only risk factor for strictures at diagnosis
        - Seen more often in adults
- Unknown if there are two phenotypes of EoE
  - Inflammatory versus structuring

**The allergist role in EoE**

- EoE is an antigen-driven allergic condition
- Common to have other atopic diseases
  - 50-90% of patients have more than one atopic disease
    - Allergic rhinitis
    - IgE-mediated food allergies
    - Asthma
- EoE may be seasonal
- EoE may be refractory if other atopic diseases are not treated
- Recommended to have allergist evaluation
Incidence of atopic symptoms

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinoconjunctivitis</td>
<td>58%</td>
</tr>
<tr>
<td>Wheezing</td>
<td>37%</td>
</tr>
<tr>
<td>Food allergy (based on clinical response, RAST or positive skin testing)</td>
<td>46%</td>
</tr>
<tr>
<td>Family history of atopy</td>
<td>74%</td>
</tr>
<tr>
<td>Family history of EoE</td>
<td>7%</td>
</tr>
</tbody>
</table>

Psychological dysfunction associated with EoE

- Able to be assessed using PedsQL™ EoE surveys
- Common
  - A review found 69% of EoE patients had some psychological dysfunction
    - Social difficulties
      - Meal time stress
      - Need for feeding tube
    - Anxiety
    - Depression
    - School problems

Monitoring and follow up

- Our current best objective measure of EoE disease activity is the number of eos/HPF
  - It is unclear if there should be no eosinophils or less than 15/hpf
- Symptoms correlate poorly with histology
- Repeat endoscopy with each change in therapy
  - Allow at least 4 weeks between each therapy change
- Repeat endoscopy if symptomatic
  - May become tolerant of topical corticosteroids
EoE—the next frontier

- Steroids with better esophageal tissue adherence
- Biologics targeting IL-13, IL-4 or eotaxin
- Less invasive mechanisms to monitor esophageal eosinophilia
  - Serum biomarkers
  - Esophageal string test
    - Capsule filled with a 90-cm string and swallowed
    - String remains in place for specified time (taped to face)
    - String is removed and the proximal secretions are evaluated for disease biomarkers
  - Nasal endoscopy
- Long term data of topical corticosteroid use and diet

Common patient scenarios

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2 yo female with long standing history of regurgitation, poor weight gain and eczema.

Patient had EGD which showed greater than 50 eos/hpf in three esophageal biopsies. Otherwise her EGD was normal. She was started on cow’s milk free diet and her repeat EGD in 8 weeks showed only 5 eos/hpf on esophageal biopsy.
14 yo male who has been to the ER three times for a food impaction after eating steak. The food impactions have resolved without medical intervention.

- EGD performed for food impaction removal. Esophageal biopsies showed >100 eos/hpf.
- Placed on PPI 40 mg twice a day and repeat EGD showed normal esophageal biopsies.

15 yo male with history of celiac disease who now complains of several months of feeling like food is getting stuck when eating. He is now on an all liquid diet (formula).

- EGD showed esophageal stricture in mid esophagus along with biopsies consistent with EoE (>60 eos/hpf).
- Repeat EGD on PPI BID showed improvement in eos/hpf (now 35 eos/hpf) but still with stricture.
- Started on swallowed budesonide therapy BID for 10 weeks. His third EGD showed improvement in stricture and no esophageal eosinophilia.
- Will consider repeating EGD on daily budesonide therapy.

Future therapies for EoE

- Anti-IL5
  - Reslizumab (open-label extension trial over 9 years)
    * Reduced median esophageal eosinophilia from 35 to 3
    * Improvement in clinical symptoms
  - Benralizumab - Anti-IL5(R) on eosinophils
    * Apoptosis by NK cells (used in asthma)
- Anti-IL13
  - Reduced esophageal eosinophils by 60%
  - Reduced some clinical symptoms
  - Effect sustained for 6 months
Future therapies for EoE

- Anti-IL4Ra
  - Inhibits IL4 and IL13
  - Reduced eosinophils by 93%
  - Improved symptoms
  - Double blind placebo controlled RCT beginning soon

Markowitz et al. JPGN 2018;66:893-897.

Take home points

- The incidence and prevalence of EoE is rising
  - Most common etiology of dysphagia in pediatrics and adults
  - Similar to other atopic diseases
- EoE is a chronic antigen-driven disease
- Initial EGD should be performed off of PPI therapy
- There are a variety of therapies for EoE
  - Elemental diet is most effective but least desirable
  - Other therapies include medications and/or diet elimination
    - PPI and/or topical corticosteroids

Take home points

- There are no clear guidelines regarding monitoring after treatment has been started
  - Should repeat endoscopy after each clinical change or symptoms return
    - Allow at least 4 weeks between EGDs
- Allergy referral recommended to treat other atopic diseases
Resources

- American Partnership for Eosinophilic Disorders (APFED)
  - www.APFED.org
- North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)
  - www.GIKids.org
- Food Allergy Research and Education (FARE)
  - www.foodallergy.org

Questions?

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References

References

• NASPGHAN EoE slideset 2014
• Straumann and Katzka Gastroenterology 2018;154:346-359.