Eosinophilic Esophagitis

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Objectives
- Learn the Definitions of
  • Esophageal Eosinophilia
  • PPI-Responsive Esophageal Eosinophilia (PPI-REE)
  • Eosinophilic Esophagitis (EOE)
- Epidemiology of EOE
- Clinical Manifestations
- Diagnostic Algorithm
- Management of EOE

INTRODUCTION
- Esophageal Eosinophilia and Eosinophilic Esophagitis (EOE) are increasingly recognized
- Commonly encountered by gastroenterologists, pathologists, and allergists
- Remarkable progress in the understanding of EOE since the time of its recognition two decades ago

Esophageal Eosinophilia
- DEFINITION – Presence of Eosinophils in the squamous epithelium of the esophagus.
- Eosinophils in Esophagus is always abnormal and the underlying cause should be identified.
- Causes of Esophageal Eosinophilia
  • Gastroesophageal Reflux Disease (GERD)
  • PPI-Responsive Esophagitis (PPI-REE)
  • Eosinophilic Esophagitis (EOE)

Diseases associated with Esophageal Eosinophilia
- Eosinophilic Gastrointestinal diseases
- Celiac disease
- Crohn’s disease
- Infection
- Hypereosinophilic syndrome
- Achalasia
- Drug hypersensitivity
- Vasculitis
- Pemphigus
- Connective tissue diseases
- Graft versus Host Disease
GERD
- Clinical symptoms of heart burn or acid regurgitation responding to PPI
  OR
- Endoscopic evidence of severe reflux esophagitis (LA class C or D)
  OR
- Positive Ambulatory PH testing (De-Meester score > 14 confirms acid reflux)

PPI-Responsive Esophageal Eosinophilia
- Symptoms related to esophageal dysfunction +
  - Histology revealing Esophageal eosinophilia with peak eosinophils > 15 cells/high power field +
  - After 8 weeks of PPI - there is BOTH Clinical and histological response (esophageal eosinophils decrease to <15 cells/hpf)

Eosinophilic Esophagitis (EOE)
- Symptoms related to esophageal dysfunction +
  - Histology revealing Esophageal eosinophilia with peak eosinophils > 15 cells/high power field +
  - After 8 weeks of PPI - there is NO Clinical and/or histological response (esophageal eosinophils decrease to <15 cells/hpf)

Epidemiology of EOE
- EOE is a chronic allergic & an T-cell immune mediated condition
- EOE involves proinflammatory mediators and chemoattractants that regulate eosinophilic accumulation in the esophagus
- Usually presents in childhood or during the third or fourth decade of life.
- The typical EoE patient is an atopic male.
  - Male preponderance. Male : Female = 3:1
  - Commonly associated with other atopic diatheses (food allergy, asthma, eczema, chronic rhinitis, environmental allergies)

CLINICAL MANIFESTATIONS
- Several clinical symptoms may be present in EOE.
- In adults, solid food dysphagia is the most common presenting symptom.
- Food impaction necessitating endoscopic bolus removal occurs in 33 – 54 % of adult EoE patients.
- Other symptoms in adults include chest pain, heartburn, and upper abdominal pain.
  "No clinical symptom is pathognomonic for EOE"

Endoscopic Findings
- Fixed esophageal rings (also called as trachealization).
- Edema (also referred to as mucosal pallor or decreased vascularity).
- Longitudinal furrows.
### Endoscopic Findings
- Diffuse esophageal narrowing.
- Whitish exudates (Plaques)
- Esophageal lacerations (a manifestation of mucosal fragility).

### Endoscopic findings are NOT pathognomonic for EoE
- A meta-analysis of endoscopic findings in EoE
  - 100 publications
  - 4,678 patients with EoE and 2,742 controls
  - Sensitivity, specificity, and predictive values of endoscopic findings alone to diagnose EoE

### Results
- Endoscopic Findings Insufficient to diagnose EoE
- The inter- and intra-observer reliability of detecting endoscopic findings WAS just about Fair
- Endoscopic appearance may be normal in 10 – 25 % of patients with EoE

### Endoscopy with Biopsy
- Endoscopy with Mucosal biopsies of the esophagus should be obtained in all patients in whom EoE is a clinical possibility regardless of the endoscopic appearance.
- Inflammatory changes in EoE are frequently patchy and may not be present in all biopsies.
- Endoscopist will obtain 2 – 4 biopsies from at least two different locations in the esophagus, most typically in the distal and proximal halves of the esophagus.

### Histologic Characteristics of EOE
- No study has determined an “exact” threshold number of eosinophils that establishes a diagnosis of EoE.

### Consensus
- ≥ 15 eosinophils in at least one microscopy high-power field on esophageal biopsy specimen
- after a 8-week PPI trial
- in the right clinical setting Consistent with the diagnosis of EoE.

### Other Histologic Features
- Eosinophil microabscess formation
- Superficial layering of eosinophils
- Extracellular eosinophil granules
- Basal cell hyperplasia
- Rete-peg elongation
- Subepithelial lamina propria fibrosis
  *None is pathognomonic for EoE

### Treatment End–Points
- Improvement in clinical symptoms & Improvement in esophageal eosinophilic inflammation
- Ideal End–point: complete resolution of symptoms and pathology.
- Practical end–point: Acceptance of a range of reductions in symptoms and histology.
Symptoms are an important parameter of response in EoE. Symptoms alone cannot be used as a reliable determinant of disease activity and response to therapy. Compensatory dietary and lifestyle factors can mask symptoms and are difficult to quantify. Esophageal strictures may not respond to medical therapy.

Topical Steroid Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Age group</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone</td>
<td>Children</td>
<td>88-440mcg/day in a divided dose</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>880-1760mcg/day in a divided dose</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Children</td>
<td>1 mg/day</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>2 mg/day, typically in a divided dose</td>
</tr>
</tbody>
</table>

EoE, eosinophilic esophagitis.

1Use a multi-dose inhaler preparation. The patient should be instructed to puff the medication into their mouth during a breath hold, and then swallow it, to minimize pulmonary deposition.

2Specific doses in children will be determined by age, height, or weight.

3Use the aqueous solution in a ratio of 1 mg/2ml budesonide mixed with 5g of sucralose for the oral viscous budesonide preparation.

Topical steroids for initial duration of 8 weeks
- Swallowed Fluticasone
- Swallowed Budesonide
- Proven to be effective
- First line therapy

Available as multi-dose inhalers or aqueous nebulizer solutions for use in asthma

Swallowed rather than inhaled to coat the esophagus and provide topical delivery

Budesonide also available as an oral viscous solution (mix aqueous budesonide with 5g sucralose – slurry)

Symptoms in eosinophilic esophagitis: Systematic review and meta-analysis of placebo-controlled randomized clinical trials

Systemic steroids
- Similar in efficacy as compared to oral fluticasone
- May even lead to a robust histologic response
- But significant increase in side effects
- In a study in Children, 40% kids has side effects (hyperphagia, weight gain, cushingoid features)

Reserved for use when topical steroids are ineffective or rapid improvement in symptoms may be needed.
Dietary Therapies

- Elemental or Amino-acid based Therapies
  - Most effective dietary therapy
  - 95–98% reduction in symptoms
  - Resolution of histology within 4 weeks in Children

- Empiric 6-food elimination diet
  - Soy, egg, milk, wheat, nuts, and seafood
  - Symptomatic and histologic resolution in 74% of a pediatric cohort

- Targeted Elimination Diet guided by Allergy Testing (usually in consultation with an allergist)
  - Skin prick test (typical)
  - Patch test

Problem with Dietary Therapies

- Labor, cost and time-intensive

- Elemental formulas are costly, often require the placement of feeding tubes for formula administration

- May impact the quality of a patient’s life.

- May not be preferred by patient and family.

- Not widely studied in Adults.

Endoscopic Dilation in EOE

- Fibro–stenotic complications
  - Focal esophageal strictures
  - Narrow–caliber esophagus

- Esophageal dilation – effective therapy in
  - Symptomatic patients with strictures that persist in spite of medical or dietary therapy, &
  - Performed initially in patients with severely symptomatic esophageal stenosis

Endoscopic Esophageal Dilation

- Several large series, esophageal dilation relieved dysphagia in majority of patients.

- Mean duration of response to dilation was more than a year.

- Post–dilation survey – Very high degree of patient acceptance for primary therapy with esophageal dilation.

- Almost all patients were willing to undergo repeated dilation as needed.

- It is preferable to reserve dilation until after the effects of medical or dietary therapy can be assessed.

- Except when
  - A critical stricture is encountered on initial endoscopy OR
  - Food impaction has occurred

- Duration of treatment is usually 4 – 8 weeks.

- Clinical improvement and endoscopy with esophageal biopsy should be used to assess the response to dietary treatment.

- If in clinical remission, step-wise reintroduction of food antigens performed.

- When food antigens are being reintroduced, both clinical symptoms and esophageal inflammation should be followed.
**Esophageal Dilation**

- Esophageal dilation must be approached conservatively
- Esophageal mucosa is extremely fragile in EoE
- Patients should be well informed of the risks of esophageal dilation in EoE including:
  - post-dilation chest pain (occurs in up to 75% pts)
  - bleeding (1%), and
  - esophageal perforation (0.3%)

**Natural History of EOE**

- EoE is a chronic disease.
- Adults may have had decades of symptoms prior to diagnosis of EoE.
- EoE may progress from an inflammatory to a fibrotic process.
- High likelihood of symptom recurrence after discontinuing treatment.

**Maintenance Therapy**

- Overall goal of maintenance therapy
  - minimize symptoms
  - prevent complications of EoE
  - preserve quality of life
  - minimal long-term adverse effects of treatments
- Maintenance therapy can be with swallowed topical corticosteroids and/or dietary restriction
- Maintenance therapy should be considered for all patients, but particularly in those
  - with severe dysphagia
  - with food impaction
  - high-grade esophageal stricture, and
  - rapid symptomatic/histologic relapse following initial therapy.

**Maintenance Therapy**

- Pharmacological Therapy
  - 1 mg/day of budesonide
  - 880 mcg/day of fluticasone (lower doses in children)
  - dose titrated to provide the best clinical response at the lowest achievable dose
- Long-term dietary elimination therapy
  - common maintenance strategy, particularly in children
  - no clinical trials of this strategy
  - large case series with good follow-up intervals support its use in children, as well as adults

**Maintenance Therapy**

- Intermittent esophageal dilation, typically in an "on-demand" fashion for recurrent symptoms of dysphagia.
- If used alone, this does not have an impact on the underlying esophageal eosinophilia.
- Can be effective for treating symptoms of dysphagia.

**TAKE HOME POINTS**

- EOE is a Clinico-Pathologic Immune mediated condition.
- The presence of Esophageal Eosinophilia alone does not mean EOE.
- To diagnose EOE, we need
  - Clinical symptoms of Esophageal Dysfunction
  - Biopsy proven Esophageal Eosinophils
  - Must persist after a PPI trial
  - Mucosal eosinophilia is isolated to the esophagus.
Topical Steroids (swallowed fluticasone or budesonide) are the first-line treatment options.

- Dietary restrictions (six food elimination diet) and systemic steroids are second line or alternative regimens.
- Esophageal dilation helps improve symptoms in patients with esophageal strictures and history of food impactions.
- Patients should be counseled about the high likelihood of symptom recurrence after discontinuing treatment due to the chronic nature of this disease.
- Low dose topical steroids maintenance regimen may be required for patients with recurrent EOE.