Eosinophilic Esophagitis

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Learning Objectives

• To define Eosinophilic Esophagitis (EoE) and present the updated 2011 diagnostic guidelines.
• To understand the epidemiology, pathophysiology and genetics of EoE.
• To identify the clinical symptoms, allergic manifestations, endoscopic and histologic features of EoE.
• To list and define the treatments of EoE which include dietary restriction, pharmacologic therapy and esophageal dilation.
• To understand how to manage patients with EoE.
• To provide information regarding ongoing and future research on EoE.
Have you seen this?

- 3 yo with poor weight gain and feeding difficulty
- 5 yo with intermittent vomiting and epigastric pain
- 8 yo with frequent regurgitation and heartburn that recurs after stopping a PPI
- 12 year old with complaints of “difficulty swallowing”
- 15 year with an “emergent” esophageal food impaction requiring immediate removal
- 28 year old with chronic heartburn and nausea
- 36 year old requiring emergent endoscopy for an esophageal food impaction

Background & Natural History
Background

- Rare cases suggestive of eosinophilic esophagitis (EoE) were described in the 1970’s
- Began to be described in early 1990’s
- Appreciated as a distinct entity in early 1990’s


Landmark article

Eosinophilic Esophagitis Attributed to Gastroesophageal Reflux: Improvement With an Amino Acid-Based Formula

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**Background**

- Initially described as EE, now EoE, several pediatric gastroenterologists (1 adult GI from Europe) first subsequently demonstrated that EoE responded not only to diet restriction but also to prednisone and swallowed topical steroids.

- Initially, unclear if EE was part of the spectrum of eosinophilic gastroenteritis.

- Allergists became involved, interested in etiology, pathogenesis and treatment of disease.

- Adult GIs in US began seeing increased food impactions & similar endoscopic findings in early to mid 2000’s.
2013 Distribution of EoE

Increase in EoE journal articles
Natural History

• In a prospective case series of 30 adults with EoE (followed for a mean of 7.2 years)
  – 29/30 persistent dysphagia
  – Biopsies and dilation performed
  – Deeper biopsy tissue was available in 7, and 6 exhibited evidence of fibrosis in the lamina propria
  – Although variable in number, all had a persistent, severe esophageal eosinophilia


Natural History – Adult Study

Definition

Gastrointestinal Eosinophils

Normal eosinophil values, per high power field (hpf):

- Esophagus (0)
- Gastric antrum (2-10)
- Duodenum (10-20)
- Colon (15-30)

Average accepted values

Esophageal Eosinophilia

Differential Diagnosis
- Eosinophilic Esophagitis
- Gastroesophageal Reflux Disease
- PPI-responsive esophageal eosinophilia
- Celiac Disease
- Eosinophilic gastroenteritis
- Crohn’s Disease
- Hypereosinophilic syndrome
- Achalasia
- Vasculitis, pemphigus, connective tissue disease
- Infection
- GVHD

Esophageal Eosinophilia is not Eosinophilic Esophagitis

2007 Consensus Recommendations Facts

- Clinical symptoms: symptoms related to GERD, dysphagia or feeding problems and poor weight gain in children and dysphagia in adults
- Natural history: Chronic disease, esophageal strictures and small caliber esophagus main morbidity
- Epidemiology: males > females; familial clustering; studies demonstrating genetic association; 1:10,000 incidence but increasing prevalence
- Allergist: essential because of association with asthma, allergic rhinitis, eczema and other food allergies

Straumann A. Gastro;125:1660,2003
Noel R. NEJM;351:940,2004
No pathognomonic endoscopic, radiologic or histologic findings

2007 Consensus Recommendations

Clinico-pathologic diagnosis

- Presence of clinical symptoms related to esophageal dysfunction
  - Vomiting, abdominal pain, heartburn, dysphagia, reflux symptoms, feeding difficulty, etc.
- Isolated esophageal eosinophilia
  - > 15 eosinophils per 40X HPF
  - Histology of remainder of GI tract normal
- Exclusion of other GI disorders
  - Absence of pathologic GERD
    - Lack of response to PPI therapy or normal pH probe
  - Infection, Crohn’s disease, hypereosinophilic syndrome

Furuta et al. Gastroenterology. 2007; 133:1342-63.
Clinico-pathologic diagnosis

- Presence of clinical symptoms related to esophageal dysfunction
  - Vomiting, abdominal pain, heartburn, dysphagia, reflux symptoms, feeding difficulty, etc.
- Isolated esophageal eosinophilia
  - ≥15 eosinophils per 40X HPF
  - Histology of remainder of GI tract normal
- Exclude other causes of esophageal eosinophilia
  - GERD
  - Exclude infection, crohn’s disease, hypereosinophilic syndrome

Need both clinical & pathologic information for proper diagnosis
Use of PPI’s help to exclude other likely disorders

Furuta et al. Gastroenterology. 2007; 133:1342-63.

2007 -2011

• Scientific publications on EoE doubled
• However .....
2011 Consensus Recommendations

- Panel of 33 physicians
- Conceptual Definition
  - “Eosinophilic esophagitis represents a chronic, immune/antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation”
- Pediatric and adult EoE very similar disease processes
  - Only difference was clinical presentation


Food Antigens Primary Cause of EoE

EoE Requires a Clinico-Pathologic Diagnosis
EoE and PPI-REE should be identified as may be distinct entity

### PPI-Responsive Esophageal Eosinophilia

#### PPI-responsive esophageal eosinophilia (PPI-REE)

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)/sex</strong></td>
<td>14/M</td>
<td>25/M</td>
<td>13/F</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Pain</td>
<td>Food impaction</td>
<td>Dysphagia</td>
</tr>
<tr>
<td><strong>Environmental Allergies</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Omeprazole 10 mg BID</td>
<td>Omeprazole 20 mg BID</td>
<td>Omeprazole 20 mg QD</td>
</tr>
<tr>
<td><strong>Eosinophils/HPF</strong></td>
<td>Before treatment</td>
<td>37</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Many other publications since 2006 have corroborated results

## PPI-REE – Estimates

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Design</th>
<th># of patients with eosinophilia treated with PPI</th>
<th>PPI-REE (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dranove</td>
<td>2009</td>
<td>Peds</td>
<td>Retro.</td>
<td>43</td>
<td>17 (40)</td>
</tr>
<tr>
<td>Sayej</td>
<td>2009</td>
<td>Peds</td>
<td>Retro.</td>
<td>36</td>
<td>14 (39)</td>
</tr>
<tr>
<td>Molina-Infante</td>
<td>2011</td>
<td>Adult</td>
<td>Prospective</td>
<td>35</td>
<td>26 (74)</td>
</tr>
<tr>
<td>Peterson</td>
<td>2010</td>
<td>Adult</td>
<td>RCT*</td>
<td>12</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Moawad</td>
<td>2011</td>
<td>Adult</td>
<td>RCT*</td>
<td>20</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Dellon</td>
<td>2013</td>
<td>Adult</td>
<td>Prospective</td>
<td>65</td>
<td>24 (37)</td>
</tr>
<tr>
<td>Schroeder</td>
<td>2013</td>
<td>Peds</td>
<td>Retro.</td>
<td>7</td>
<td>5 (71)</td>
</tr>
</tbody>
</table>


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## PPI-Responsive Esophageal Eosinophilia

- PPI-REE currently considered to be “distinct” from EoE

- **Etiology**
  - Is it due to gastroesophageal reflux responsive to acid suppression?
  - Is it a possible new anti-inflammatory effect of PPI’s?
  - Is it a subset of EoE?
  - Is it a combination of the above?

- Further research needed
Epidemiology of Eosinophilic Esophagitis

Age of Onset of EoE

Early 2000’s incidence of 10 in 100,000
Last 5 years incidence reported to have increased to 20-40 in 100,000
Prevalence continuing to increase - approaching 90-100 in 100,000

EoE patients have a unique gene expression profile

230 Genes Downregulated

344 Genes Upregulated

EoE - Genetics

- Increased incidence in siblings and 1st degree relatives
- Identified gene locus at chromosome 5q22
- TSLP gene (Thymic Stromal Lymphopoetin Protein)

**Probable Pathophysiology of EoE**

- Intraluminal allergen exposure
  - Food >>>> Aeroallergens
- Cell mediated disease (not IgE)
- Systemic etiology - not topical
- Leads to mucosal production of eosinophilic chemo-attractants
  - Influx of eosinophils
  - Release of inflammatory mediators
  - Esophageal dysfunction


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**Cells & Cytokines Related to EoE**

- Esophageal eosinophils – primary identifier
  - An expansion of Th2 lymphocytes
  - Esophageal mast cells
  - Esophageal basophils
- Cytokines
  - IL-5 and Eotaxin - primary
  - IL-4, IL-13, TSLP, TGFβ and pSMAD
Is EoE an IgE mediated Disease?

• In murine models, IgE knockout mice had no effect on disease
• SPT/Immunocap and Microarray do not work well (<15%)
• Omalizumab does not work
• Few studies with oral immunotherapy may in fact induce EoE (egg, dairy, nut)
• Recent studies identifying IgG4
  – Increased granular deposits of IgG4
  – Increased IgG4 plasma cells
  – Increased serum IgG4 to specific food antigens

Fibrosis
**Esophageal Fibrosis**

- Occurs in animal models
  - In response to allergen challenge
- Occurs in pediatric and adult patients
  - With dysphagia, esophageal rings, strictures
- Components of EoE remodeling
  - Fibrosis, Collagen deposition, Pro-fibrotic factors, Pro-fibrotic signaling molecules, Angiogenesis, Vascular activation


**EoE as a Progressive Disease**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Predicted probability of developing fibrostenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>20</td>
<td>0.2</td>
</tr>
<tr>
<td>30</td>
<td>0.3</td>
</tr>
<tr>
<td>40</td>
<td>0.4</td>
</tr>
<tr>
<td>50</td>
<td>0.5</td>
</tr>
<tr>
<td>60</td>
<td>0.6</td>
</tr>
<tr>
<td>70</td>
<td>0.7</td>
</tr>
<tr>
<td>80</td>
<td>0.8</td>
</tr>
</tbody>
</table>

OR = 2.1 (1.7-2.7) per 10 year increase for developing a fibrostenotic EoE phenotype

EoE and Atopy

Prevalence of Atopic Disease in EoE

- 50-60% of EoE patients have one or more of the following:
  - Asthma
  - Allergic rhinitis
  - Atopic dermatitis
  - Other IgE mediated food allergies
### Prevalence of Atopy

<table>
<thead>
<tr>
<th>Author/population</th>
<th>Number of patients with EoE</th>
<th>Asthma</th>
<th>Allergic Rhinitis</th>
<th>Atopic Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy in the General Population</td>
<td></td>
<td>8.5%</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>Spergel, et al; Philadelphia</td>
<td>620</td>
<td>50%</td>
<td>61%</td>
<td>21%</td>
</tr>
<tr>
<td>Assa’ad, et al; Cincinnati</td>
<td>89</td>
<td>39%</td>
<td>30%</td>
<td>19%</td>
</tr>
<tr>
<td>Sugnanam, et al; Australia</td>
<td>45</td>
<td>66%</td>
<td>93%</td>
<td>55%</td>
</tr>
<tr>
<td>Guajardo, et al; World Wide Registry</td>
<td>39</td>
<td>38%</td>
<td>64%</td>
<td>26%</td>
</tr>
</tbody>
</table>


### Association with Environmental Allergies
### Seasonal Variation in EoE

20 year old female, history of multi-sensitization to aeroallergens. Symptoms of allergy and EoE peaked during pollen season.


### Allergic rhinitis and EoE

- Proximal esophageal eosinophils were found in
  - 0 control patients
  - 10 (26%) with allergic rhinitis
- Eosinophils per HPF
  - 9.5 ± 7.3 in allergic rhinitis patients
- Proximal esophagus only
- Resolved with use of nasal fluticasone

Liacouras et al, 2014 abstract
Pediatric Clinical Symptoms

Clinical Features

- Male predominance (about 3:1)
- Multiple reports of familial clustering (within and across generations)
- Association with food allergy and atopy
- Chronic condition in adults and children

Furuta et al. Gastroenterology. 2007; 133:1342-1363.
Feeding Disorder: 13%
Vomiting: 26%
Abdominal Pain: 26%
Dysphagia: 27%
Food Impaction: 7%

Clinical Symptoms – Epigastric Pain

- Present in 5-68% of children
- Frequent, but not universal complaint
- May be chest pain or abdominal pain (epigastric or generalized)
- GERD-like symptoms in 5-82% of children
- Odynophagia is not typical
- May be responsive to acid suppression therapy
**Clinical Symptoms - Vomiting**

- Present in 8-100% of children with EoE
- Not clinically distinguishable from other causes of vomiting
- Symptom frequently misclassified as GERD and there is often a delay in diagnosis
- Typically true vomiting over effortless regurgitation
- Chronic, episodic and unpredictable
- May not occur immediately after food ingestion

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**Clinical Symptoms - Dysphagia**

- The most common symptom of EoE in adults
- In children, dysphagia manifests in several ways:
  - Choking, gagging, food refusal
  - The sensation of food sticking or going down slowly
  - Food impaction
- Often difficult to obtain an accurate history in children
- Occurs even in the absence of esophageal stricture or small caliber esophagus
Adult Clinical Symptoms

Presenting Symptoms of EoE in Adults

- Dysphagia ($p>0.2^*$)
- GERD/Heartburn ($p>0.2^*$)
- Abdominal Pain, Dyspepsia, N/V ($p>0.2^*$)

* $P$ value for $\chi^2$ comparing the proportion of males vs. females

Radiologic Findings

Esophageal Rings
Small Caliber Esophagus

Endoscopic Findings
Normal Esophagus

Esophageal Furrowing
Esophageal Rings

White Plaques
Small Caliber Esophagus

EoE can wax and wane

M.M. 1961, Plumber
- 2000 Onset of dysphagia and diagnosis of EE
- 2006 February 26th: Still symptomatic
- 2006 May 3rd: Screening examination for study

>150 Eos/HPF
12 Eos/HPF
EoE Can progress quickly

W.A. 1978, Software Engineer
- 2004 Onset of Dysphagia: Endoscopy Sept 2nd
- 2005 Still symptomatic: Endoscopy Sept 8th

White Esophagus
224 Eos/hpf

Lacerations
86 Eos/hpf

Histology of EoE
Normal Histology

EoE Histology
Eosinophilic Esophagitis

Severe Eosinophilia

Superficial Layering

Eosinophilic Microabscess

Eosinophilia is often patchy

Multiple biopsies are necessary

EoE currently determined by the number of eosinophils in most affected field

Histology of EoE
Overall Goals:

- Alleviation of presenting symptoms
- Prevention of disease recurrence
- Improvement in quality of life
- Prevent complications

Management Options for EoE

• After EoE is diagnosed by clinicians, taking into consideration all clinical and pathologic information, treatment choices are:

- Elimination Diet
- Combination of Diet and Steroids
- Elemental Diet
- Combination of Diet with Elemental Supplementation
- Esophageal Dilation
- Steroids Topical or Systemic
- Pharmacologic Therapy
- Nutrition Therapy

Savary Esophageal Dilators

Laceration After Dilation in EoE

Hirano C. Foreign Bodies in the Esophagus. In: Shields, LoCicero, Feir^~
Reed, eds. General Thoracic Surgery 7th Ed. Lippincott Williams & Wilk
Publ. Chapter 149.
Esophageal Dilation in EoE

- Dilation does not address the underlying disease process
- Relapse is common after dilation although prolonged remission can occur
- Significant risk of long mucosal lacerations and pain
- Esophageal perforation risk is low but consequences can be substantial
- Pharmacologic and dietary therapy is effective at relieving symptoms and treating strictures

*Whenever possible, pharmacologic or dietary therapy should be attempted prior to esophageal dilation as both reverse EoE*


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Steroid Treatment in Pediatrics
Oral Steroid Studies

1 mg/kg BID; max 30 mg BID


Topical Corticosteroids

- Initial report by Faubion et al, in 1998, in 4 children
- Fluticasone now a common therapy
- Demonstrated improved symptoms and histology
- Side effects not common, and often mild (*Candidiasis* can be seen)

**Topical Steroids (Swallowed Fluticasone)**

<table>
<thead>
<tr>
<th>Design</th>
<th>Max Dose</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konikoff (n=18)</td>
<td>880 mcg/day</td>
<td>84.6</td>
<td>19.7</td>
</tr>
<tr>
<td>Noel (n=20)</td>
<td>1320 mcg/day</td>
<td>43.4</td>
<td>1</td>
</tr>
<tr>
<td>Teitelbaum (n=13)</td>
<td>880 mcg/day</td>
<td>23</td>
<td>2.7</td>
</tr>
<tr>
<td>Schaefer (n=40)</td>
<td>1760 mcg/day</td>
<td>33.3</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*Post treatment data on 16 patients.


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**White Plaques Before and After Treatment**
Liquid Budesonide

- Problems with topical fluticasone
  - Difficult to administer
  - Not totally delivered to esophagus
- Advantages of a liquid preparation
  - Easier to administer
  - Close to 100% administered
  - Better topical agent
  - No significant adverse effects; esophageal Candidiasis in one patient


Randomized, Double-Blind Placebo Controlled Trial Budesonide (BEE Trial)

36 Patients with EoE
Placebo or budesonide 1 mg BID x 15 days

Before treatment
After treatment

Guidelines for Corticosteroids in EoE

- Systemic and topical corticosteroids effectively resolve the acute clinico-pathological features of EoE.
- When discontinued, the disease generally recurs.
- Systemic corticosteroids may be utilized in emergent cases such as dysphagia requiring hospitalization, dehydration due to swallowing difficulties and weight loss, etc.
  - Because of the potential for significant toxicity their long-term use is not recommended.
- Topical corticosteroids are effective in inducing a remission of EoE when utilized in high doses (pediatrics & adults).
  - The incidence of long-term side effects with this form of administration has not been formally studied but currently it is well tolerated (fungal infections).
- Topical corticosteroids are used for maintenance of EoE – in process of long-term studies.

Furuta et al. Gastroenterology. 2007; 133:1342-63.
History of Diet and EoE

• In 1995: “Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula”
  – 10 patients with refractory reflux symptoms, despite medication
  – 6 had received anti-reflux surgery without resolution
  – All with markedly elevated esophageal eosinophils
• Patients given a trial of an “elemental diet”
  – Amino acid based formula
  – Minimized any risk of food allergy


Diet and Eosinophilic Esophagitis

• After elemental diet:
  – Symptom resolution in 8 patients, improvement in 2
  – Improvement occurred within 3 weeks
  – Biopsies improved as well
• Symptoms returned after food was reintroduced
• Conclusions:
  – EoE is an allergic phenomenon
  – EoE improves with food elimination
Dietary Management
Amino Acid–Based Formula

- 172 Patients (128 nasogastric tube, 32 oral, 4 failed, 8 noncompliant)
  - 160 patients completed therapy
- Patients evaluated 4-6 weeks after instituting diet

<table>
<thead>
<tr>
<th>160 Patients</th>
<th>Pre-diet</th>
<th>Post-diet</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophils per hpf</td>
<td>38.7 ± 10.3</td>
<td>1.1 ± 0.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>30</td>
<td>1</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>GERD symptoms</td>
<td>134</td>
<td>3</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>


EoE – Elemental Diet

Before
After
Amino Acid Based Formulas in Adults

• Peterson et al. (2013)
  – Group of adults on an elemental diet
  – 70% with histologic response to < 10 eos/hpf
  – 50% with histologic response to normal (few or no eos)
  – Problems
    ▪ Symptomatic response difficult
    ▪ Problems with assessment tool
    ▪ Problems with compliance

Advantages of Amino Acid Based Diet

• Extremely effective therapy for EoE
• Great for patients with FTT, young children and for those in which no other therapy is effective
• When administered correctly:
  – > 95-98% demonstrate complete clinical and histologic response
  – Allows systematic re-introduction of foods
• Shown to be effective for anyone - adolescents and adults
### Obstacles to Elemental Diet

- Elemental formula is unpalatable
- Commonly needs nasogastric or gastrostomy tube to administer
- Nutritional status must be monitored closely - DIETICIAN
- Elemental formulas are expensive
  - Variable insurance coverage
  - Usually significant out of pocket expense
- Concern regarding quality of life issues

### Other Types of Dietary Therapy for EoE

- Selective Diet
  - Empiric Diet
  - Directed (Targeted) Diet
Empiric (SFED) Elimination Diet

- Six food elimination diet (SFED)
- 60 EoE patients – retrospective review but compared
  - 35 given diet without milk, soy, wheat, egg, peanut, nut and fish
  - 25 given amino acid formula
- Biopsies done at start compared with 6 weeks of diet therapy
- Improvement in restricted group 75% while amino acid group 90+%
Empiric Diet Elimination

- **Benefits**
  - Easy, do not need testing

- **Problems**
  - May not eliminate all foods necessary to induce remission
  - May eliminate foods that are not necessary to be eliminated
  - May prolong the process of food elimination and re-introduction

Allergy Food Testing in EoE

Serum IgE tests
Allergy Food Testing in EoE

• Despite pathogenesis of EoE not being an IgE related disease

• Some investigators have used the combination of skin prick tests (SPT) and atopy patch tests (APT) to identify causative foods
  – To be effective need to be very experienced with the use of patch testing

• Problems
  – SPT only identify IgE mediated allergy - not etiology of EoE but could have association
  – Serum IgE tests – EoE not IgE mediated
  – APT not a standardized test – each investigator often preparing test and reading test differently – hard to duplicate results

Allergy Testing vs Empiric Histology

Rodriguez-Sanchez et al. Allergy 2014
Microarray Testing in EoE

- 40 adults
- Diet based on microarray IgE testing
- Compared to Immunocap, specific IgE testing
- No significant response
- IgE testing ineffective

van Rhijn et al J Allergy Clin Immunol 2015

What method is best?

Diet Success

Spergel et al J Allergy Clin Immunol 2012; 130:461-7
Response of 3 Types of Dietary Restriction


Guidelines for Dietary Therapy in EoE

- Dietary therapy (AA formula, SFED, directed diet) should be considered and discussed in all patients – ADULTS & CHILDREN – who have a diagnosis of EoE

- Many adults with EoE are interested in diet therapy

- Dietary therapy has also been shown to reverse esophageal fibrosis.

- All modes of dietary therapy successful in children and adults

- Allergists important for dietary treatment and for other associated atopic disease

- For ALL dietary therapy, consultation with a registered dietician is strongly recommended to ensure proper calories and micronutrients.