Eosinophilic gastrointestinal diseases

Professor Frank Thien
Monash University and Eastern Health, Melbourne Australia
APAAACI Congress
October 19th 2016
Causes of Eosinophilia

Table 2. Proposed classification and differential diagnosis of eosinophilic gastroenteritis.

<table>
<thead>
<tr>
<th>Primary eosinophilic gastroenteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal</td>
</tr>
<tr>
<td>Muscular</td>
</tr>
<tr>
<td>Serosal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary eosinophilic gastroenteritis and/or differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Hypereosinophilia syndrome</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Autoimmune disease, vasculitis</td>
</tr>
<tr>
<td>Connective tissue disease</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Transplantation</td>
</tr>
<tr>
<td>Inflammatory fibroid polyps</td>
</tr>
</tbody>
</table>
Primary gastrointestinal Eosinophilic disease

• Eosinophilic esophagitis → Increasing prevalence with recent advances in diagnosis and management

• Eosinophilic gastritis
• Eosinophilic enteritis
• Eosinophilic colitis

Uncommon rare diagnoses
Background

• A person with Eosinophilic esophagitis (EoE) presents with dysphagia, food bolus obstruction or retrosternal discomfort.

• Diagnosis is made at gastroscopy; >15 eosinophils per high power field
Background

• The pathological changes are typically; eosinophil rich inflammation, epithelial hyperplasia and muscular hypertrophy and hyperplasia.

• This is thought to represent an inflammatory response to food or aeroallergens
Eosinophilic esophagitis histopathology

**Eosinophilic Esophagitis**
- Epithelial hyperplasia
- Angiogenesis
- Disruption of barrier integrity
- Muscular hypertrophy and hyperplasia

**Normal Esophagus**
- Epithelial surface
- Capillary
- Lamina propria
- Muscularis mucosae
- Eosinophil (transmural inflammation)

*Philpott et al. Clinical and Experimental Allergy; 2014: 44 (8) 1012 – 19*
Prevalence of pediatric and adult EoE

- Adult prevalence
  - USA Olmsted County: 55/100,000
  - USA nationwide: 58.9/100,000
  - Switzerland, Europe: 43/100,000

- Pediatric prevalence
  - USA Hamilton County: 43/100,000
  - USA nationwide: 50.5/100,000
  - Switzerland, Europe: 6/100,000

References:
- Prasad et al, Clin Gastroenterol Hepatol 2009
- Noel RJ et al, NEJM 2004
- Hruz P et al, JACI 2011
- Dellon ES et al, Gastroenterol Hepatol 2014

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Background

- EoE is becoming increasingly common, with an estimated prevalence of 50 per 100,000. This parallels a rise in allergic conditions per se.
Characterization of inflammatory pattern

Cellular components involved in EoE
• Eosinophils, different sets of T cells and mast cells

Mediators involved in EoE
• IL-4, IL-5, IL-13 and TNFα

EoE has mainly a Th2-type inflammatory pattern

Strauman A et al JACI 2001
Gupta SK et al JPGN 2006
The end result of unchecked inflammation is stricture formation and food bolus obstruction.

Straumann et al. GASTROENTEROLOGY 2003;125:1660–1669
Delay in Diagnosis of Eosinophilic Esophagitis Increases Risk for Stricture Formation in a Time-Dependent Manner

ALAIN M. SCHÖEPFER,1,* EKATERINA SAFRONEEVA,2,* CHRISTIAN BUSSMANN,3 TANJA KUCHEN,4 SUSANNE PORTMANN,5 HANS-UWE SIMON,6 and ALEX STRAUMANN7,8

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GASTROENTEROLOGY 2013;145:1230–1236

Figure 3. Percentage of patients without strictures during the diagnostic delay period encompassing >20 years.
Advances in Eosinophilic Esophagitis Diagnosis and Management

• Recognition of Proton-Pump Inhibitor Responsive Eosinophilic Esophagitis (PPI-REE)

• Recognition of efficacy of 6 Food Elimination Diet (6FED)

• Role of Allergy Tests
A. EoE and GERD – an evolution

1. **Pre-1993**: All cases of esophageal inflammation with eosinophils are GERD or infection

2. Attwood (1993) distinct entity of eosinophilic esophagitis and patients presenting for fundoplication with no GERD (pH studies are performed)

3. Patients with esophageal eosinophilia responsive to PPI’s with/without GERD (PPI-REE) (2011)

4. All patients with esophageal eosinophilia should have BD PPI’s for diagnostic/therapeutic purposes (2013)

*PPI = proton pump inhibitors
*PPI – REE = esophageal eosinophilia that disappears with 8 weeks of PPI’s

Clinicians think about EoE and use oral fluticasone

Clinicians think about using PPI’s
Advances in Eosinophilic Esophagitis Diagnosis and Management

• Recognition of Proton-Pump Inhibitor Responsive Eosinophilic Esophagitis (PPI-REE)

• Recognition of efficacy of 6 Food Elimination Diet (6FED)

• Role of Allergy Tests
What happens if the esophagus is protected from antigens

Empiric 6 food elimination diet

• (Milk, wheat, eggs, nuts, soy and seafood) for 6 weeks

Symptoms

• Significant improvement in 70-94% of patients

Histology

• Resolution of eosinophilic inflammation in > 70%

Kagalwalla A et al CGH 2006
Gonsalves N et al Gastro 2012
What happens when the esophagus is re-exposed to antigens

Stepwise and controlled re-introduction of food

Gonsalves N et al Gastro 2012
Which food categories are critical?

Stepwise reintroduction identified offending foods

- Wheat 60%
- Milk 50%
- Soy 10%
- Nuts 10%
- Egg 5%
- Seafood 0%

Role of IgE?

SPT and Specific IgE accurately predicted only 13% of offending foods

Kagalwalla A et al CGH 2006
Gonsalves N et al Gastro 2012
B. EoE and Diet

**Recommendations**

13. Dietary elimination can be considered as an initial therapy in the treatment of pediatric and adult EoE. (Strong recommendation, evidence moderate)

**Figure 4.** The efficacy of SFEDs in inducing histologic remission (<15 eosinophils/hpf) in patients with EoE.
Elimination Diet Effectively Treats Eosinophilic Esophagitis in Adults; Food Reintroduction Identifies Causative Factors

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GASTROENTEROLOGY 2012;142:1451–1459

<table>
<thead>
<tr>
<th>Table 1. Patient Demographics and Clinical Characteristics</th>
</tr>
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<tbody>
<tr>
<td><strong>Patients completing the</strong></td>
</tr>
<tr>
<td>SFED (N = 50)</td>
</tr>
<tr>
<td>Mean age, y (range)</td>
</tr>
<tr>
<td>Presenting symptom</td>
</tr>
<tr>
<td>Dysphagia</td>
</tr>
<tr>
<td>Food impaction</td>
</tr>
<tr>
<td>Heartburn</td>
</tr>
<tr>
<td>Duration of symptoms (range)</td>
</tr>
<tr>
<td>Endoscopy features</td>
</tr>
<tr>
<td>Concentric rings</td>
</tr>
<tr>
<td>Linear furrows</td>
</tr>
<tr>
<td>Stricture</td>
</tr>
<tr>
<td>Exudates/plaques</td>
</tr>
<tr>
<td>Ethnicity</td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>African American</td>
</tr>
<tr>
<td>Presence of atopy (asthma, allergic rhinitis, allergic conjunctivitis, sinusitis, or eczema)</td>
</tr>
</tbody>
</table>

*study over 5 years

*variable PPI use

*gastroscopy monthly intervals after 2 food groups

*no reason stated for drop out 40 patients.
67 initiated 8 food elimination diet
37 had complete response
Variable PPI use
22 completed reintroduction with food identification*
6 that were followed up over 3 years = durable response
A real world study of patients presenting with dysphagia/dyspepia and esophageal eosinophilia

Dr Hamish Philpott et al
Monash University
Eastern Health
Patients with eosophageal eosinophilia

- *gastroscopy*

EoE

- *gastroscopy*

6FED

- *gastroscopy*

Response

- *Repeat gastroscopy (3 months)*

- *Maintain diet (avoid culprit food)*

- *Repeat gastroscopy (3 months)*

- *Continue process of dietary reintroduction*

- *Repeat gastroscopy (3 months)*

Esomeprazole 40mg Po BD commenced and continued for all patients

Responses:
- Either or
  - *gastroscopy*
  - *Repeat gastroscopy (3 months)*

- *Budesonide*
Process and order of dietary reintroduction in patients initially responding to the 6FED. Foods are eaten at least daily, gastroscopy performed at 2 weeks following food introduction.

If recurrence of eosinophilia is detected, the culprit food is removed and a 4 week (wash-out) interval occurs before repeat.
<table>
<thead>
<tr>
<th>Index</th>
<th>All (n=107)</th>
<th>PPI-REE (n=25)</th>
<th>EoE (n=82)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>37 (10.2) y</td>
<td>44 (14)</td>
<td>34 (11)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Mean age (SD) at diagnosis</td>
<td>34 (14) y</td>
<td>42 (11)</td>
<td>32 (10)</td>
<td>&lt;.05</td>
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<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
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<tr>
<td>White Caucasian</td>
<td>105 (96%)</td>
<td>23 (92%)</td>
<td>80 (98%)</td>
<td>NS</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (2%)</td>
<td>1 (4%)</td>
<td>1 (1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>2 (2%)</td>
<td>1 (4%)</td>
<td>1 (1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of atopic illness</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Seasonal rhinitis</td>
<td>52 (47%)</td>
<td>16 (58%)</td>
<td>36 (44%)</td>
<td>&lt;.05</td>
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<tr>
<td>Asthma</td>
<td>21 (19%)</td>
<td>5 (20%)</td>
<td>16 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Food allergy or oral-food allergy syndrome</td>
<td>9 (8%)</td>
<td>3 (12%)</td>
<td>6 (7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Helicobacter pylori positive (at initial endoscopy post 8 weeks of BD esomeprazole)</td>
<td>4 (4%)</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Presenting symptom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food bolus obstruction</td>
<td>47 (43%)</td>
<td>16 (64%)</td>
<td>31 (38%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>FBOE and dysphagia</td>
<td>30 (27.5%)</td>
<td>5 (20%)</td>
<td>25 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Dysphagia alone</td>
<td>22 (20%)</td>
<td>3 (8%)</td>
<td>19 (23%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Heartburn</td>
<td>5 (4.5%)</td>
<td>1 (1%)</td>
<td>4 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>4 (4%)</td>
<td>0</td>
<td>4 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous treatment of oesophageal eosinophilia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI – daily</td>
<td>78 (72%)</td>
<td>12 (48%)</td>
<td>66 (80%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>PPI – BD</td>
<td>14 (13%)</td>
<td>4 (16%)</td>
<td>8 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Swallowed topically-acting corticosteroid</td>
<td>43 (40%)</td>
<td>8 (32%)</td>
<td>35 (43%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diet</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
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</tbody>
</table>
107 patients with eosophageal eosinophilia

PPI – REE
25 patients

gastroscopy

EoE
– 82 patients

Budesonide 25 patients

25/25 (92%)

Failed 6FED 29/56

Multiple gastroscopies

Continue dietary reintroduction

36% (20/56) Identify food triggers

3 fail to identify food triggers

6 drop out

4 drop out

Response to budesonide 23/25 (92%)

1 drop out

Response to 6FED – 29/56 (52%)

Identify food triggers

Esomeprazole 40mg Po BD commenced and continued for all patients

6 drop out

1 drop out

29/56 (52%)

23/25 (92%)

4 drop out
### 1. Initial Group

- **107 patients with oesophageal eosinophilia**

  - Gastroscopy
    - PPI-responsive (n=25)
    - EoE (n=81)
  - Drop-out (n=1)

### 2. Treatment Groups

- **81 patients with EoE choose diet with PPI or budesonide monotherapy**

  - Elimination diet + PPI (n=56)
  - Budesonide primary therapy (n=25)

  - Gastroscopy
    - 29/56 respond (52%)
    - 23/25 respond (92%)

### 3. Dietary Reintroduction

- **29 patients undergo dietary reintroduction**

  - Food triggers found (n=20)
  - No trigger (n=3)

  - Gastroscopy @ 3 months
    - 88% in remission
    - 78% in remission
  - Cease follow-up

  - Gastroscopy @ 9 months
    - 7/18 (39%) cease treatment
    - 10/18 (55%) in remission
    - 1/18 (5%) drop out

### 4. Budesonide Treatment

- **Budesonide primary therapy**

  - Elimination diet + PPI
  - PPI monotherapy

  - Gastroscopy @ 3 months
    - 87% in remission
    - Cease follow-up

  - Gastroscopy @ 9 months
    - 7/18 (39%) cease treatment

- **Budesonide (secondary therapy for failed elimination diet)**

  - n=25 of 27

  - Drop-out (n=2)
  - Response (n=23, 92%)
  - No response (n=2)
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y), sex</th>
<th>Food Triggers identified at gastroscopy</th>
<th>IgE mediated measures</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SPr</td>
<td>SPE</td>
</tr>
<tr>
<td>1</td>
<td>55, female</td>
<td>Gluten†</td>
<td>rye</td>
<td>rye</td>
</tr>
<tr>
<td>2</td>
<td>58, female</td>
<td>gluten</td>
<td>rye</td>
<td>rye</td>
</tr>
<tr>
<td>3</td>
<td>21, male</td>
<td>gluten</td>
<td>rye, HDM</td>
<td>rye, HDM</td>
</tr>
<tr>
<td>4</td>
<td>44, female</td>
<td>gluten</td>
<td>rye</td>
<td>rye</td>
</tr>
<tr>
<td>5</td>
<td>54, female</td>
<td>gluten</td>
<td>rye</td>
<td>HDM</td>
</tr>
<tr>
<td>6</td>
<td>29, male</td>
<td>gluten</td>
<td>wheat</td>
<td>Peanut, soy, wheat</td>
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<tr>
<td>7</td>
<td>62, male</td>
<td>Dairy</td>
<td>milk*</td>
<td>milk</td>
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<tr>
<td>8</td>
<td>19, male</td>
<td>Dairy</td>
<td>rye, HDM</td>
<td>rye</td>
</tr>
<tr>
<td>9</td>
<td>61, male</td>
<td>Dairy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>19, male</td>
<td>Egg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>19, male</td>
<td>egg</td>
<td>rye</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>64, male</td>
<td>Soy</td>
<td>birch, HDM, rye</td>
<td>birch, rye</td>
</tr>
<tr>
<td>13</td>
<td>49, female</td>
<td>Dairy, egg, gluten, nut</td>
<td>rye, HDM, milk</td>
<td>rye, nut</td>
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<tr>
<td>14</td>
<td>27, male</td>
<td>Nut, fish</td>
<td>rye</td>
<td>rye</td>
</tr>
<tr>
<td>15</td>
<td>33, female</td>
<td>Dairy, egg</td>
<td>rye</td>
<td>rye</td>
</tr>
<tr>
<td>16</td>
<td>52, male</td>
<td>Dairy, egg</td>
<td>HDM</td>
<td>milk, egg, HDM</td>
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<tr>
<td>17</td>
<td>48, male</td>
<td>gluten, egg, dairy</td>
<td>milk</td>
<td>milk, rye</td>
</tr>
<tr>
<td>18</td>
<td>19, female</td>
<td>Egg</td>
<td>rye, wheat, rye</td>
<td>peanut, soy**</td>
</tr>
</tbody>
</table>
Results

• 25% had PPI – REE. 80% in remission 3 months

• Budesonide group – 90% complete response, 80% in remission 3 months

• Diet group – 52% complete response BUT:
  – significant drop out during reintroduction phase
  – 80% remission 3 months
  – only 50% of those in remission remain on treatment at 9 months
Real World Outcomes

• Clinicians can expect many of their patients (previously treated) to respond to PPIs (1 in 3)

• 6FED in patients with variable access to dieticians will induce remission in just over 50%, and only 50% of those initially achieving remission will stay compliant and controlled at 9 months

• Budesonide is, by contrast is a very effective therapy
## GERD, PPI-REE & EoE

<table>
<thead>
<tr>
<th></th>
<th>GERD</th>
<th>PPI-REE</th>
<th>EoE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Gastric content reflux</td>
<td>Unknown</td>
<td>Food/airborne allergens</td>
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<tr>
<td></td>
<td>Not expressed</td>
<td>Overexpressed</td>
<td>Overexpressed</td>
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<tr>
<td><strong>Symptoms</strong></td>
<td>Heartburn, regurgitation, dysphagia</td>
<td>Dysphagia, food bolus impaction</td>
<td>Dysphagia, food bolus impaction</td>
</tr>
<tr>
<td></td>
<td>Distal</td>
<td>Distal and proximal</td>
<td>Distal and proximal</td>
</tr>
<tr>
<td></td>
<td>80% increased acid exposure in erosive GERD</td>
<td>70% increased/30% normal acid exposure</td>
<td>60% normal/40% increased acid exposure</td>
</tr>
<tr>
<td></td>
<td>50% normal acid exposure in non erosive GERD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of immune</strong></td>
<td>Th1</td>
<td>Th2</td>
<td>Th2</td>
</tr>
<tr>
<td>response/involved</td>
<td>IL-8, MCP-1, RANTES</td>
<td>Eotaxin-3, IL-13, IL-5</td>
<td>Eotaxin-3, IL-13, IL-5</td>
</tr>
<tr>
<td>chemo/cytokines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inflammatory cells</strong></td>
<td>Neutrophils, lymphocytes, low-grade eosinophilia</td>
<td>Eosinophils and mast cells</td>
<td>Eosinophils and mast cells</td>
</tr>
<tr>
<td></td>
<td>PPI therapy fundoplication surgery</td>
<td>PPI therapy</td>
<td>Steroids/diet</td>
</tr>
</tbody>
</table>

*EoE* eosinophilic esophagitis, *GERD* gastroesophageal reflux disease, *PPI* proton pump inhibitor, *PPI-REE* proton pump inhibitor-responsive esophageal eosinophilia

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Molina-Infante *et al* Curr Treat Options in Gastro 2015
Advances in Eosinophilic Esophagitis Diagnosis and Management

• Recognition of Proton-Pump Inhibitor Responsive Eosinophilic Esophagitis (PPI-REE)

• Recognition of efficacy of 6 Food Elimination Diet (6FED)

• Role of Allergy Tests
The role of allergy tests?

• Most adult experts do not recommend performing allergy tests to determine dietary therapy.

• Allergy consultation reasonable to assess often associated atopic disease
Allergy Tests

SPa (skin patch) = cell mediated?

SPr (Skin prick) allergic sensitisation?

Basophil activation test (BAT)
Our experience of allergy tests

- 108 patients received Skin prick test and food/aeroallergen specific IgE (wheat, milk, egg, soy, peanut, tuna fish, birch pollen, rye grass and dust mite)

- 26 patients in addition received skin patch test, basophil activation test and IgG antibody tests to same allergens.
Our EoE allergy test study

Prospective

• Utilise 5 methodologies; Skin prick, Skin Patch, Specific IgE, Basophil activation tests & IgG4

Allergy tests do not predict food triggers in adult patients with eosinophilic oesophagitis. A comprehensive prospective study using five modalities

H. Philpott*†‡, S. Nandurkar*†, S. G. Royce*, F. Thien*† & P. R. Gibson*†
## Current pharmacotherapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pharmacological targets</th>
<th>Evidence Base</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Multiple</td>
<td>Randomised controlled trial(88)</td>
<td>50-90% response</td>
</tr>
<tr>
<td>Monteleukast</td>
<td>Leukotriene receptor</td>
<td>Open label trial(92)</td>
<td>ineffective</td>
</tr>
<tr>
<td>Sodium cromoglycate</td>
<td>Mast cell</td>
<td>Case report(12)</td>
<td>ineffective</td>
</tr>
<tr>
<td>Thiopurines (azathioprine)</td>
<td></td>
<td>Case report(93)</td>
<td>effective</td>
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<tr>
<td>Mepolizumab</td>
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<td>Ineffective</td>
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<td>CRTH2 receptor</td>
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<tr>
<td>Losartan</td>
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<td>?</td>
</tr>
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</table>

*Philpott et al. Pharmacology and Therapeutics 2014*
Summary

• 1st step in all patients – start high dose PPI and re-scope for PPI-REE

• Dietary therapy is a reasonable alternative, adherence 50% at 9 months

• Allergy tests are not useful.
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