Financial disclosures:

- Janssen
- Genetech
- UCB
- All for research support
Learning Objectives

- To identify the clinical symptoms, allergic associations
- To define histologic features
- To review the epidemiology, pathophysiology and genetics of EoE
- To list and define the treatments of EoE
- To understand what is successful treatment
- Look at the value of long term treatment
Which age group has the highest prevalence of EoE?

- A) 15- 39 years
- B) 39 – 49 years
- C) 49- 65 years
- D) 5 – 15 years

Answer: A
Prevalence of EOE by age
Rise in EoE
Relevance of EoE for IM

- Main cause of dysphagia in young adults in Europe and North America
- Second only to GERD as the most prevalent cause of esophageal symptoms
- Annual expenditure for EoE is about the same as IBD, GI bleeding (>1 billion)
- Mean delay in diagnosis in adults is 7 years
- Under diagnosed!
Pathogenesis of EoE

Figure 1: Pathogenesis of Eosinophilic esophagitis
Why do we worry about EoE?
Evolution of EoE

- Early Adopters/Pioneers
- Mass Market/Followers
- End of Life

Diagram showing the evolution of endoscopic features at EoE diagnosis over different diagnostic delay periods.
Small caliber esophagus
Atopy and EoE overlap

- Asthma 35 to 50% *
- Allergic rhinitis 20 to 60% *
- Atopic dermatitis 10 to 40%
- Anaphylaxis 1% to 15%
- Overall, 50 to 60% have some atopy
- Rise in atopy mirrors rise in EoE
- Could control of extra esophageal atopy help control EoE?
Cellular tight junctions

- Mucus layer
- Apical side
- Basolateral surface
- Tight junctions
- Lumen
- Apical side
- Plasma membrane
- Basolateral side
- Paracellular space
- Protein complex
  - Occludin
  - Claudin 1
  - E-cadherin
  - ZO-1
  - JAM-1
  - Catenins
  - Cingulin
  - Actin
Inflammation in EoE

Figure 2: Physiological diagram [44].

Adapted from Simon HU, Straumann A., Immunopathogenesis of eosinophilic esophagitis. Dig Dis. 2014;32(1-2):11-4
Importance of Eosinophils

Eosinophil Biology

Eosinophil granule proteins
- major basic protein
- eosinophil derived neurotoxin
- eosinophil cationic protein
- eosinophil peroxidase

Cytokines

Arachidonic acid products

Neurotransmitters

Allergen or other stimulus
Issues of remodeling

- Chronic eosinophilic inflammation is associated with tissue remodeling.
- Inflammatory changes in EoE are transmural
- Sub epithelial fibrosis and smooth muscle hypertrophy and hyperplasia
- Smooth muscle dysfunction
- Tissue sampling may not determine fibrosis
Effect on smooth muscle

- Vigorous achalasia, DES, nutcracker esophagus, high amplitude contractions, simultaneous contractions, contractions during sleep and interprandial periods
- MBP is agonist to acetylcholine
- Mast cells have histamine (+Ach)
- Some evidence that early disease is hyperkinetic and longer standing disease is hypokinetic
Normal Esophageal Biopsy
Eosinophil Tissue Remodeling
Sub epithelial fibrosis
DIAGNOSIS OF EOE
Which of the following is true in the diagnosis of EoE?

1) Diagnosis of EoE is based on finding of > 15 eosinophils/hpf *
2) Biopsies are taken from the distal esophagus
3) Heartburn is not a symptom of EoE
4) Eosinophilia is not found in GERD
5) EoE should be considered in all patients with dysphagia

Answer: 5
Diagnosis- no gold standard

- **Clinicopathologic** diagnosis encompassing:
  - Symptoms related to esophageal dysfunction
  - Eosinophil predominant inflammation >15 eos
  - Mucosal eosinophilia limited to esophagus and persists after a PPI trial
  - Secondary causes of eosinophilia excluded
  - Response to treatment supports, but is not required for diagnosis
  - Biopsies should be taken from both proximal and distal portion of the esophagus
Epidemiology and Natural History

- North American, Europe, and Australia
- 3 to 4:1 Men to Women
- Prevalence is 52/100,000
- 1 new case per 10,000 per year
- Prevalence is Factors: decreased H.P., increased PPI use, early life antibiotics, rise in connective tissue and autoimmune diseases, hygiene hypothesis, microbiome, food sources, antibiotics and fertilizers tin food, arid and/or cold climate
Clinical symptoms

- Dysphagia/impaction *
- Chest pain
- Modification of eating
- Heartburn
- Globus
- Abdominal pain
- Weight loss
- Family history of EoE
- Associated disorders (allergy, atopic diseases, asthma)
EGD

- At least 4 biopsies from the upper and 4 from lower esophagus
- Location noted
- Disease is patchy on H&E
- Visual suggestions in about 50%
- Eosinophilia only in the distal esophagus could be GERD
Biopsies for EoE

Eosinophilic esophagitis:
Number of biopsies to make diagnosis

Gonsalves et al, Gastrointest Endosc 2006; 64: 31
Esophageal Eosinophilia is not EoE

- EoE
- GERD *
- PPI responsive EoE
- Celiac
- Crohn’s disease
- Hypereosinophilic syndrome
- Achalasia
- Vasculitis, pemphigus, connective tissue
- Infectious
- GVHD
- Eosinophilic gastroenteritis
EOE TREATMENT TARGETS
What should be the initial treatment in EoE?

- Systemic steroids
- Topical steroids
- PPI
- Elemental diet
- 6 food elimination diet

Answer: PPI treatment
Therapeutic endpoints

- Histology
- Symptoms
- Quality of life
- Complications
- Endoscopy
- Esophageal compliance
EoE treatment options

Pharmacologic therapy
- Corticosteroids (systemic; topical)
- PPI therapy
- Leukotriene antagonists (montelukast)
- Mast cell stabilizer
- Immunomodulators (6 MP, azathioprine)
- Biologics (anti-IL-5, Anti-IL-13)

Dietary Therapy

Allergy evaluation

Endoscopic therapy
Dietary Therapy In EoE
Elemental diet

- Outperforms all other therapy options (>90%) including steroids
- Adherence
- Psychological/Social impact
- Not recommended as first line therapy
- Tastes terrible
- Insurance issues- high cost
- Relapse
Allergy Testing

- Skin prick and atopy patch testing
- "False positive" occurs in 50-60% of SPT
- Response rate about 30%
- Serum food-specific IgE
- Not an IgE based disease
- Effectiveness 50% children, about 35% in adults
Dietary therapy- SFED

- Milk, wheat, egg, soy, nuts, seafood/shellfish
- 70 to 75% effectiveness
- May become FFED- add shellfish and nuts (~70%)
- Wheat and milk are most common allergens
- Reintroduction of food and repeat EGD in 8 weeks
- Generally considered preferred tx option after PPI-REE
Food Elimination in EOE

- Milk: 74%
- Wheat: 26%
- Egg: 17%
- Soy: 10%
- Peanut/Treenut: 6%
- Seafood: 0%
Sequential Reintroduction and Monitoring

- Add selected food after histologic remission
- Absence of symptoms does not imply remission of disease
- Remission phase: 6 to 8 week trial and adherence is very important followed by EGD
- Food reintroduction: with regular consumption followed by EGD
- Maintenance phase: Avoidance of specific foods to maintain disease remission. Studies show effectiveness for up to 5 years
Dilation for EoE
Dilation therapy

- Early literature reported concerns
- Subsequent studies showed good safety profile
- Patients- 74% report chest pain following exam
- Expensive and has risks
- Does not alter disease progression
- Effective and robust treatment for a significant stricture
DRUGS
Proton Pump Inhibitor responsive Esophageal Eosinophilia

- Indistinguishable endoscopic, clinical, genetic, histology or treatment
- Equal response to steroids and PPI
- PPI is anti-inflammatory and down regulates Eotaxin-3
- Both groups respond to dietary restrictions and have similar pH results
Issues of Drugs

- Unavailability of drugs specifically approved
- Chronic disease would require long term treatment
- Absence of long term data
- No evidence for prevention of complications (e.g. fibrosis)
EoE vs. GERD – May be inseparable?

A Complex relationship

Diagram showing the relationship between GERD and EoE over time.
PPI mechanism – it’s complicated

- Acid reflux may weaken the integrity between cells
- PPI down regulates eotaxin -3, IL-6, IL-8, and TNF-alpha
- ACG recommends 2 month PPI trial and repeat biopsy with repeat biopsy
- May have long term effectiveness
PPI-REE; more than antacids

- Clinical, histologic and genetic analysis do not distinguish EoE from GERD.
- May be subset of EoE
- Appears to have long term effectiveness
- 50-60% response rate overall
- Usually dosed BID
- Needs EGD to confirm response
Steroids

- Slurry, swallowed inhaler or systemic
- Fluticasone 220 mcg inhaler, 4 puffs BID
- Budesonide 1 mg BID mixed with thickening agent
- Relapse in majority
- Long term consequence is unknown
- Tips for most effective use:
  - for MDI, swallow meds w/ breath hold
  - NPO x 30-60 minutes after
  - 8 weeks treatment followed by EGD
Maintenance Therapy
Long term therapy

- Maintenance therapy should be considered in all patients
- Inflammation returns after therapy withdrawn
- Long term outcome unknown
- Should long term include EGD evaluation?
- Does histologic control imply prevention of fibrosis