Disclosures:

Moderator:
Kenneth R. DeVault, MD, FACP
Board of Directors: Mayo Clinic
Consultant: Phathom Pharmaceuticals
Research Grant: Ironwood (multicenter study site), Phathom (central reading of endoscopy images)

Speakers:
Kathryn Peterson, MD, MSCI (EPID)
Consultant: Alaxos, Astra Zeneca, Regeneron;
Board Member/License Holder/Stockholder: Nexeos Inc.

Amiko Uchida, MD
Dr. Uchida has Nothing to Disclose

Off Label Usage:
Dupilumab for EOE and EGID
AK002 for EGID and EOE
Topical steroids are not FDA approved so any mention would be off label now

Eosinophilic Esophagitis and Eosinophilic GI Diseases: Pearls and Pitfalls

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University of Utah School of Medicine

Amiko Uchida, MD
Massachusetts General Hospital
Eosinophilic Esophagitis

1978

1993

2003
Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. PMID: 14724818 Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Gastroenterol. 2003 Dec;125(6):1660.

EoE Symptoms

- Acid reflux
- Dysphagia
- Chest pain
- Nausea/vomiting
- Early satiety
- Food impaction

EoE Pathophysiology

Environment
- Birth/Childhood factors
- Seasonality
- H Pylori

Genetics

Food/Aeroallergen

Compromised barrier

EPITHELIUM
- Desmoglein
- Filaggrin
- Calpain 14

Dendritic cell

Antigen Presentation

LAMINA PROPIA
- +TH2
- IL-13
- Fibroblast

Periostin

TGF BETA

FIBROSIS

TSLP

Basophil

IL-9

Mast Cell

Eosinophil

IL-13

IL-5

Compromised barrier

EoE Endoscopic Reference Score (EREFS)

Edema (loss vascular markings)
- Grade 0: Distinct vascularity
- Grade 1: Decreased
- Grade 2: Absent

Rings (trachealization)
- Grade 0: None
- Grade 1: Mild (ridges)
- Grade 2: Moderate (distinct rings)
- Grade 3: Severe (not pass scope)

Exudate (white plaques)
- Grade 0: None
- Grade 1: Mild (<10% surface area)
- Grade 2: Severe (>10% surface area)

Furrows (vertical lines)
- Grade 0: None
- Grade 1: Mild
- Grade 2: Severe (depth)

Stricture
- Grade 0: Absent
- Grade 1: Present
Endoscopic evaluation in EoE:

- Allows for characterization of esophageal abnormalities that can be identified in over 95% of adolescent/adult patients (Dellon, Gastro 2017, Lucendo Gastro 2019)

- Endoscopy provides gross, “whole organ” assessment of inflammatory and fibrostenotic activity

- High degree of accuracy in adults (SN 88%, SP 92%; Dellon Clin Gastro Hepatol 2015) and children (SN 90%; SP 88%, Wechsler Clin Gastro Hep 2018)

- Complements assessment of therapeutic outcomes in EoE that are currently based on symptoms and pathology

Symptoms alone not enough

- Only modest correlation with dz
  - Adaptive behavior
  - Connective tissue disease
  - Underlying motility disorder
  - Fibrosis
  - Mast cells
Histology alone is not enough

Diagnostic Conundrum:
Reliance upon histopathology alone

15 eosinophils/HPF
EoE Treatment Options

- **PPI**
  - At least 30% of EoE patients are responsive to PPI
- **Topical Steroids**
  - Fluticasone (puff swallowed daily), Budesonide Slurry
- **Routine Dilations**
- **Diet**
  - Food Elimination
  - Hypoallergenic elemental diet if there is not remission with above treatments, overall >90% effective
- **Biologics**
Diet: AGA guidelines 2020

• The expert panel noted that the consideration of a testing-based diet would be made in the context of other management options, including other dietary management options, such as elemental or empiric dietary elimination.

Meta-analysis of Dietary Interventions for Histologic Remission in EoE

• Only 1 in 6 adults with improvement after allergy testing directed diet

• Other studies show approximately only 30% were found to achieve histologic remission (≤15 eos/ hpf) after undergoing allergy testing–directed diets for 6 weeks

Overall effectiveness

- Elemental 90.8%
- SFED 72.1%
- Food elimin 45.5%

Atopy Patch Tests?

- Prospective study with SFED at Mayo
- 50% of patients with positive APT
- Only 16% had foods on APT tested positive for causative food in EoE

- Sens 6%
- Specificity 92%

Efficacy of Atopy Patch Testing in Directed Dietary Therapy of Eosinophilic Esophagitis: A Pilot Study. Eckmann JD1, Ravi K2, Katzka DA2, Davis DR3, See JA4, Geno DR2, Kryser LA2, Alexander JA5

Six Food Elimination Diet

- Elimination of Top 6 allergens: Dairy, Wheat, Egg, Soy, Peanut/Tree Nut, Fish/Shellfish
  - Overall SFED remission rate: 66-78% of patients
    - Cow’s milk (74% children, 50% adult)
    - Wheat (26%, 60%)
    - Egg (17%, 10%)
    - Soy (10%, 10%)
    - Peanut (6%, 5%)

SFED Protocol

EoE Diagnosis → PPI trial (8 weeks) → SFED

EGD after 6-8 weeks on SFED

Introduce 1-2 least likely trigger foods (usually seafood and nuts)

EGD after 4-6 weeks

Introduce 1-2 foods (egg and soy)

EGD after 4-6 weeks

Introduce Wheat

EGD after 4-6 weeks

Introduce Dairy

Step-up (2-4-6) Elimination Diet

• Multi-center prospective study in Spain of children and adults (n=130):
  • 2 food (no milk, gluten for 6 weeks): 43% (n=56/130) 6 weeks
    • Of 56: 52% milk, 16% gluten, 28% both 6 weeks
  • 4 food (no milk, gluten, egg, soy/legumes): 60% 6 weeks
  • 6 food (no milk, gluten, egg, soy/legumes, nuts, fish): 79% 6 weeks
Elimination Dietary Education Considerations

- Dairy: Sheep and goat are generally not safe for cow’s milk protein allergy
- Wheat vs. Gluten: Non-wheat gluten products have the potential for cross-contamination. As well as cross-reactivity--Spanish studies exclude gluten.
- Soy: Soy Lecithin is OKAY on SFED
- Coconut is OKAY on SFED
- What if patient fails SFED

Steroid Treatment

- Topical (induce remission in up to 80% of patients)
  - Budesonide
  - Fluticasone
- Carrier vehicles
  - Honey
  - Syrup
  - Xanthan gum
- Maintenance???
Biologics

In Phase II and Phase III studies

• Dupilumab: anti-IL4R (blocks IL-4 and IL-13)

• RPC 4046: anti-IL13 mAb

• Benralizumab and Mepolizumab: anti-IL5R and anti-IL5, respectively

Dupilumab (Anti-IL4R) reduced dysphagia, esophageal eosinophilia and endoscopic activity in a recent phase 2 study in adults with EoE

Symptoms

Pathology

Endoscopy

Placebo
(n/N = 14/24)

Dupilumab 300 mg every week
(n/N = 17/23)

LS = Least Squares; SDI = Straumann Dysphagia Index; Eosinophilic Esophagitis Endoscopic Reference Score; SE = Standard Error


Hirano Dellon Gastroenterology 2020
EoE “PLUS”

Things to consider...

EGID: Symptoms

- Acid reflux
- Dysphagia
- Chest pain
- Nausea/vomiting
- Early satiety
- Food impaction
- Refractory abdominal pain
- Bloat
- Loose stool
- Malnutrition/PLE
- “Dyspepsia and IBS”

Atopic Disease in EoE

- 90.6% of patients with atopy
- 67% food allergy
- 60.3% allergic rhinitis
- 46.4% atopic dermatitis
- 45.4% asthma
- 31.2% allergic conjunctivitis
- 26.2% urticaria
- 27.1% food anaphylaxis
- 13.2% angioedema

Why allergists should be involved

- Anaphylaxis
- Pollen Food Allergy Syndrome
- Drug Allergy
- Latex Allergy

- Consortium survey with reported up to 10% of EOE with Eos gastritis (EG)

- UPDB familial data shows evidence of increased risk of EG and EGE out to second degree relatives of patients with EOE

Gastric Eosinophils

- Infection
- *H. pylori*
- Crohn’s
- Drugs
- Tumors
- Connective tissue diseases
- Food Allergy
- Hematopoetic disorder or systemic eosinophil disorder
Endoscopic Findings of EGID Variable


Over 60% without endoscopic findings!!!

CAN BE NORMAL

Why is EG/EGE so difficult?

- What is normal?
- Duodenum
  - Quantified that 20 eos/HPF considered probably abnormal
  - **susicion**
  - Studies more stringent
  - Dyspepsia conundrum
- Stomach
  - 30 eos/HPF over 5 HPF

Diagnosis of eosinophilic gastroenteritis is easily missed

Kadjo-Kmosa Alassa, Xian-Yi Lin, Xie-Ying Xuan, Hao-Xiong Zhou, Yan-Wei Gao
**Treatment for EGID**

- Systematic review
- Most small series or cases
  - N = 30, pediatric
- Elemental diets with 75.8% improvement
  - Clinical improvement
- Histological assessments not commonly done

**Adults**
- Data mixed with steroids
  - 12/21 responded in one retrospective study
  - Azathioprine for steroid dependence
  - Small study

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**Esophageal Eosinophilia:**
excluding other causes (drug reaction, EGPA, HES, parasite)

- Functional symptoms such as IBS/Dyspepsia, abdominal pain
- Biopsy for EG/EGE
- Labs for associated conditions:
  - Tryptase
  - Autoimmune
  - Immune d/o
- Work up for other eos d/o
- More diffuse disease
  - Diet
  - Systemic meds

- No functional symptoms
  - PPI BID* TCS Elimination diet

  - EGD
    - <15 eos
      - Sx gone
      - Long term PPI/TCS maintenance
      - Attempt to wean
      - Food reintroduction (4-6 w)
    - <15 eos
      - Sx present
      - Alternative reasons
        - Mast cell dz
        - Granule Proteins
        - Stricture
  - >15 eos
    - Sx present
    - Switch to other therapy (add on)
      - Attempt to wean
      - Increase food elimination
      - Food elimination + TCS
      - Biologics

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Putting it together...

Case 1: 40-year-old female with EoE and refractory abdominal pain

- You scope a 40 yo female with EoE and dyspepsia. She is on PPI for EoE and no other meds.
- EoE is resolved on endoscopy E1R1E0F0S0
- In the stomach you see the following...
Follow-up

- You perform 4 biopsies in antrum and 4 in body and rule out H Pylori
- There is non-specific inflammation

- Ask for eosinophil counts
- Biopsies demonstrate eosinophils/ HPF
- 40, 29, 30, 31, 35 in antrum
- 20, 15, 10, 36, 45 eos/HPF in body

Case 2: 34-year-old male with dysphagia

- Presented for initial endoscopy (top panel) with 50 eosinophils/HPF and E1R0E2F2S1

- Started elimination diet and all follow up endoscopies with low EREFS scores and no symptoms (below)
2 years later no symptoms
- eos 35/HPF

Shared decision making**

Case 3: 36-year-old male with Tryptase 22
One shoe does not fit all sizes...

1. Distal esophagus > 100 eosinophils per HPF
2. Proximal esophagus > 100 eosinophils per HPF
1. Proximal esophagus: nonspecific reactive changes and occasional intraepithelial eosinophils
2. Distal esophagus: focal acute inflammation and non-specific reactive changes

 Role of Mast Cells with Symptoms

- Mast cells in histologic remission

New Science and Data in EoE and EGID

Anti-IL13 Ab decreases epithelial mesenchymal transition
Anti-IL13 Ab decreases epithelial mesenchymal transition

E-cadherin - epithelial
Vimentin - mesenchymal

Antifibrotic effects of Thiazolidinediones

+/- Rosiglitazone (TZD)
+/- TGFb

Culture esophageal Fibroblasts from Healthy or EoE pts

qPCR for profibrotic transcripts

Quan M. Nhu, MD, PhD, Lenice Hsiu, BS, Lucas Dohil, BS, Ranjan Dohil, MD, Robert D. Newbury, MD, Richard Kurten, PhD, Fouad J. Mowad, MD and Seema S. Aceves, MD, PhD. Clinical Translational Gastroenterology. April 2020. Antifibrotic Effects of the Thiazolidinediones in Eosinophilic Esophagitis Pathologic Remodeling: A Preclinical Evaluation
Pre-clinical Study with Thiazolidinediones

TZDs selectively decrease pro-fibrotic markers in EoE primary fibroblasts

The role of the mast cell in EoE

- Mast cells in smooth muscle of EoE patients express TGF-b
- Mast cells are associated with persistent dysphagia despite absent eosinophils
- Mast cells infiltrate esophageal epithelium in EoE (active and remission)

Aceves et al JACI 2010
Bolton et al AJG 2020
Strasser et al Histopathology 2018
Mast cells contribute to epithelial dysfunction

Mast Cell Activation Media

IgE/algE

24 hours

ALI Esophageal epithelial cell culture

“leaky” cellular connections

Increased intra-epithelial mast cell density in children with EoE with low eosinophil counts but persistently abnormal mucosa

Reduced Transepithelial Electrical Resistance (leaky) with exposure to mast cell degranulation media for 24 hours.

Lorena A. Ostilla1, Amanda A. Wenzel2, Ming Wang3, Brooke Boyer3, Kathryn Kerley2, Amanda B. Muir2, Marie-Pier Tetreault2, Joshua B. Wechsler
1 Pediatrics, Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, Illinois, United States; 2 Northwestern Feinberg School of Medicine, Chicago, Illinois, United States; 3 Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania, United States
Mast cells produce type 2 cytokines

Tissue mast cells from EGID patients have high frequencies of activated MCs and high levels of IL-13 & IL-5.

AK002 in EoE and EGID

- AK002 is a Siglec-8 antibody.
  - Targets eosinophils and mast cells for antibody-dependent cell cytotoxicity
- AK002 decreased MC degranulation and cytokine production.
- Currently in early clinical trials for EGID - ENIGMA.
Summary

• Symptoms ≠ histopathology
• PPI then steroid vs step-up diet elimination
• Skin and serum allergy testing is not helpful to guide diet elimination
• Consider fibrosis, mast cells, and alternative diagnoses with refractory symptoms.
• New therapeutics in the pipeline

Thank You!

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Questions?

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