Editorial Board Announces New Position

AJG SOCIAL MEDIA EDITOR

Social media has permanently transformed how gastroenterologists communicate, learn, and stay abreast of the latest science in our field.

We are excited to announce this new position for a highly skilled, creative, and forward-thinking gastroenterologist or hepatologist to help grow the digital footprint of AJG.

Submit Your Application!

View the full job description and application requirements: gi.org/ajgsocial

www.amjgastro.com

AJG Special Issue!

WOMEN’S HEALTH in GASTROENTEROLOGY and HEPATOLOGY

The American Journal of Gastroenterology requests your high-quality, clinically relevant research about the burden of digestive disease in women. We will collect the very best original studies and clinical reviews into a special issue highlighting this vital area of our field.

Submit Your Manuscript!

DEADLINE: AUGUST 1, 2020

The ACG Edgar Achkar Visiting Professorship Program provides an opportunity for a national expert to visit your institution, spend time with your fellows, educate colleagues, and visit with young faculty as mentors.

Deadline: Friday, July 17, 2020

Get Training in Leadership and Advocacy

Learn more: www.gi.org/yplsp
Deadline: Friday July 10, 2020

For Eligible: 3rd & 4th Year Fellows
& Physicians <5 years out of fellowship
ACG Telehealth Survey
Your Input Needed

Telehealth Usage in GI: Before, During and After COVID-19

Check Your Inbox for this Important ACG Member Survey
Your Feedback Will Help Shape the #Future of GI

Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.
How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2020 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2021 for this activity.

ACG will submit MOC points on the first of each month. Please allow 3-5 business days for your MOC credit to appear on your ABIM account.

MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.
ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

Week 15: Management of Anti Coagulation for GI Endoscopy
Aasma Shaukat, MD, MPH, FACG
July 2, 2020 at Noon EDT

Week 16: Managing Complications of Cirrhosis
Mitchell L. Shiffman, MD, FACG
July 9, 2020 at Noon EDT

Weeks 17, 18, and 19 have also been added!
Visit gi.org/ACGVGR to Register

Disclosures:

Moderator:
Kenneth R. DeVault, MD, FACG
Board of Directors: Mayo Clinic
Consultant: Phathom Pharmaceuticals
Research Grant: Ironwood; Ironwood Multicenter study where we are a site Phathom Central reading of endoscopy images

Speakers:
Kathryn Peterson, MD, MSCI (EPID)
Consultant for Allakos and Astra Zeneca and Regeneron;
Nexeos Inc. hold license to an imaging modality I will discuss and I have stock and am a board member

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

Kathryn Peterson, MD, MSCI (EPID)  
University of Utah School of Medicine

Amiko Uchida, MD  
Massachusetts General Hospital

Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. PMID: 8420741

1978
1982

Intraepithelial eosinophils: a new diagnostic criterion for reflux esophagitis. PMID: 7106512

Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. PMID: 14724818

1993

Eosinophilic Esophagitis
New Kid on the Block

Guidelines and Diagnostic Criteria

≥15 eosinophils/HPF

American College of Gastroenterology
**EoE Symptoms**

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

**EoE Pathophysiology**

1. **Environment**
   - Birth/Childhood factors
   - Seasonality
   - H Pylori

2. **Genetics**

3. **Food/Aeroallergen**

4. **Compromised barrier**

   - Epithelium
   - Lamina Propria

   - Dendritic cell
   - Antigen Presentation

   - Desmoglein
   - Filaggrin
   - Calpain 14

   - Eotaxin-3
   - TSLP

   - Basophil
   - IL-9
   - Mast Cell
   - Eosinophil

   - IL-4
   - IL-13
   - IL-5
   - IL-10
   - TGF Beta
   - Periostin
   - Plasma

   - IgG4

   - FIBROSIS

American College of Gastroenterology

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

- 100 eos/HPF
- 0 eos/HPF
- 100 eos/HPF

American College of Gastroenterology
Diagnostic Conundrum:
Reliance upon histopathology alone

15 eosinophils/HPF

First Endoscopy  
Follow up Endoscopy

EREFS alone is not enough
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 JD, Ravi K2, Katzka DA2, Davis DR3, See JA4, Geno DR2, Kryzer LA2, Alexander LE5

American College of Gastroenterology
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
  - 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**

<table>
<thead>
<tr>
<th></th>
<th>Week 10</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-4</td>
<td>-4.25</td>
</tr>
<tr>
<td>Dupilumab 300 mg every week</td>
<td>-3.5</td>
<td>-3.75</td>
</tr>
</tbody>
</table>

**Pathology**

<table>
<thead>
<tr>
<th></th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS mean ± SE change in eosinophil count</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Endoscopy**

<table>
<thead>
<tr>
<th></th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS mean ± SE change from baseline in EREPS score</td>
<td>2.5</td>
</tr>
</tbody>
</table>


**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”


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**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

- 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
- Hematopoietic disorder or systemic eosinophil disorder


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
    - **suspicion**
  - Studies more stringent
  - Dyspepsia conundrum

- Stomach
  - 30 eos/HPF over 5 HPF

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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

- No functional symptoms
  - PPI BID*
  - TCS
  - Elimination diet

Pt choice

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

- More diffuse disease
  - Diet
  - Systemic meds

6 weeks - 8 weeks
TCS = topical corticosteroid

Putting it together...

Cases
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

5 months post therapy

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

**An anti-IL-13 antibody reverses epithelial-mesenchymal transition biomarkers in eosinophilic esophagitis: phase 2 trial results**

**Primary Biomarker Outcome**

- Reduction in vimentin positive cells
  - 37.4% for 300 mg
  - 10.6% for 180 mg
  - 9.4% for placebo

- P<0.032; high dose vs placebo

**Biopsies were evaluated using an average of 47,000 cells per biopsy, avoiding biased selection of regions for analysis.**

**Effects of RPC4046, an anti-IL-13 monoclonal antibody, on EMT biomarkers in adults with active EOE**

- E-cadherin - epithelial
- Vimentin - mesenchymal

Peter H. Gaens, MD; SoO, Ryan J. Devlin, BA; Nathan McIntosh, BS; Margaret H. Collins, MD; Evan S. Dellen, MD, MPH; Iusa Hialeo, MD; Steven Ye Hua, PhD; Cristian Rodriguez, MD; Sarah Harris, PhD

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**Virtual Grand Rounds**

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

**Unmixed image**

**Markup with machine learning**

**Pt. 144**

**Baseline**

**Pt. 144**

**Week 16 (high dose RPC4046)**

**E-cadherin - epithelial**

**Vimentin - mesenchymal**
Antifibrotic effects of Thiazolidinediones

+/− Rosiglitazone (TZD)
+/− TGFβ

Culture esophageal Fibroblasts from Healthy or EoE pts

qPCR for profibrotic transcripts

Quan M. Nhu, MD, PhD, Lance Hsieh, BS, Lucas Dohil, BS, Ranjan Dohil, MD, Robert D. Newbury, MD, Richard Kurten, PhD, Fouad J. Mouawad, MD and Seema S. Aceves, MD, PhD. Clinical Translational Gastroenterology. April 2020. Antifibrotic Effects of the Thiazolidinediones in Eosinophilic Esophageal Pathology: Remodeling: A Preclinical Evaluation

Preclinical Study with Thiazolidinediones

TZDs selectively decrease pro-fibrotic markers in EoE primary fibroblasts

Quan M. Nhu et al. 2020. CTG.
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 AIG 2020
Strasser et al Histopathology 2018

Mast cells contribute to epithelial dysfunction

Mast Cell Activation Media → IgE/aIgE → 24 hours
ALI Esophageal epithelial cell culture → “leaky” cellular connections

Lorena Á. Ostilla1, Amanda A. Wenzel1, Ming Wang1, Brooke Boyer1, 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 University Feinberg School of Medicine, Chicago, Illinois, United States; 3 Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania, United States
Mast cells contribute to epithelial dysfunction

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.

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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