Welcome to the Virtual Grand Rounds Waiting Room. The educational activity will begin promptly at 12 Noon Eastern.
Welcome to the Virtual Grand Rounds Waiting Room – The educational activity will begin promptly at 12 Noon Eastern.
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.
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 37: Choledochal Cysts: Recognition and Management
Laith H. Jamil, MD, FACG
December 17, 2020 at Noon EDT

Week 1, 2021: Management of Acute Kidney Injury in Patients with Cirrhosis
Paul Y. Kwo, MD, FACG
January 7, 2021 at Noon EDT
Visit gi.org/ACGVGR to Register

Disclosures:
Speaker:
Ikuo Hirano, MD, FACG
Clinical Trials Support: Celgene/Receptos, Regeneron, Shire/Takeda, Adare, Alkaphos
Consultants: Adare, Alkaphos, Arerna, AstreaZeneca, Celgene/Receptos, Eli Lilly, Esccop, Gossamer Bio, Parexel, Regeneron, Shire/Takeda

Moderator:
Christine Y. Hachem, MD, FACG
Dr. Hachem has no conflicts of interest related to this talk.

Off Label Discussion: Use of topical steroids and PPI
New Therapeutic Options for EoE and EGIDs on the Horizon

Ikuo Hirano, MD, FACG
Gastroenterology Division
Northwestern University Medical School

OHSU Best of DDW 2016

New Therapeutic Options for Eosinophilic Gastrointestinal Disease

• What's wrong with symptom-based management in EoE?
• What's new with the "old" therapeutic options for EoE?
• How do we manage refractory EoE?
• How do we treat EGIDs outside of the esophagus?

Virtual Grand Rounds

Case: 28 yo man with progressive dysphagia. Admission for esophageal tear post endoscopic food disimpaction

EGD on PPI with severe rings. Unable to pass standard endoscope. Biopsies: 94 eos/hpf
Case: 28 yo man with progressive dysphagia. Admission for esophageal tear post endoscopic food disimpaction

EGD on PPI with severe rings. Unable to pass standard endoscope. Biopsies: 94 eos/hpf

Post Fluticasone 880 mcg BID
Continued dysphagia.

Biopsies: 94 eos/hpf

Continued dysphagia.

Biopsies: 0 eos/hpf

EGD scope not traverse.
EoE Disease Activity: More than Just Counting Eosinophils!

Activity = Inflammation + Tissue Remodeling

- Esophageal Eosinophilia
- Mucosa/submucosa/muscularis expansion, Subepithelial fibrosis, Increased vascularity, Dysmotility


Treat to Target

- **Symptoms**: Resolution of dysphagia without the need to avoid food based on texture
- **Histopathology**: Resolution of esophageal eosinophilic inflammation (< 5-15 eos/hpf)
- **Endoscopy**: Improvement in inflammatory features and strictures (Diameter > 15 mm)

Hirano, Furuta. Gastroenterology 2020;158:840-851

<table>
<thead>
<tr>
<th>Symptom Activity</th>
<th>Histologic Activity</th>
<th>Endoscopic Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>Minimum</td>
<td>Minimum</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
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</tr>
</tbody>
</table>

Complete Response

Complete Non-Response

American College of Gastroenterology
EoE Treatment Failure: Medical Therapy
Persistent symptoms and EGD signs with normal histology

EGD on PPI with severe rings. Unable to pass standard endoscope. Biopsies: 94 eos/hpf

Post Fluticasone 880 mcg BID x 6 mos. Continued dysphagia. Biopsies: 0 eos/hpf EGD scope not traverse.

Treat to Target: Symptoms, EGD, Pathology

EGD on pantoprazole 40 mg BID; weekly dysphagia. Path 100 eos/hpf

EGD on fluticasone powder 1 mg BID; No dysphagia; Path 3 eos/hpf

EoE Treatment Failure: Monotherapy with esophageal dilation
Persistent pathology with improved symptoms and endoscopy

American College of Gastroenterology
New Therapeutic Options for Eosinophilic Gastrointestinal Disease

• What’s wrong with symptom-based management in EoE?
• What’s new with the “old” therapeutic options for EoE?
• How do we manage refractory EoE?
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2020 ACG Virtual Grand Rounds on Eosinophilic Gastrointestinal Disease

• 6/25/20 – Kathy Peterson - EOE and EGID: Pearls and Pitfalls
• 9/10/20 – Gary Falk has been invited - Management of EoE With Topical steroids: The When and How of Long-Term Management
• 10/22/20 – Nirmala Gonsalves - Special Considerations When Discussing Diet Elimination for EoE
• 12/10/20 – Ikuo Hirano - New Therapeutic Options for EoE and EGIDs on the Horizon

Case Presentation: Patient JS
A 33-year-old man with history of allergic rhinitis and childhood asthma presents with an 8-year history of progressive dysphagia to meats and bread with recent ER food impaction.

The mucosa demonstrated edema, furrows, rings and exudates. Biopsies from the distal esophagus demonstrated 90 eos/HPF.
Case presentation
Which of the following statements regarding choice of initial therapy for EoE is most accurate?

a. Targeted elimination diets based on IgE based allergy testing are more effective than empiric six food elimination diets
b. To be effective in EoE, proton pump inhibitor therapy should be prescribed at double dose administered BID
c. Systemic corticosteroids are more effective at improving eosinophilic inflammation than swallowed topical corticosteroids
d. Systemic adverse effects are common with swallowed topical corticosteroids
e. In clinical guidelines, swallowed topical corticosteroids are the only initial therapeutic option for EoE recommended based on randomized, placebo-controlled clinical trials

Initial Therapeutic Choices for EoE
Medications
• Proton pump inhibition
• Swallowed topical corticosteroids
• Clinical trials
Diet therapy
• Elemental diet
• Empiric elimination diet
• Allergy-testing directed diet
Esophageal dilation
• For patients with symptomatic esophageal stricture
• Does not address underlying inflammatory process
AGA-JTF Guidelines: Management of Eosinophilic Esophagitis

Proton pump inhibition in EoE

Recommendation: In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using PPI over no treatment (conditional recommendation, very low quality evidence).

Overall, unweighted histologic response rate (<15 eos/hpf): 42%

Forest plot for not achieving histologic remission


Swallowed Topical Corticosteroid Therapy

- 8 double-blind, placebo-controlled RCTs in 437 patients
- Overall, unweighted histologic response rate (<15 eos/hpf): 65%
- Strong recommendation based on moderate quality evidence

<table>
<thead>
<tr>
<th>Study in Reference</th>
<th>Patients</th>
<th>Placebo</th>
<th>Overall, unweighted histologic response rate (&lt;15 eos/hpf)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander 2012</td>
<td>24-22</td>
<td>21</td>
<td>1.76 (95% CI: 1.39)</td>
</tr>
<tr>
<td>Buz 2014</td>
<td>27-25</td>
<td>22</td>
<td>1.58 (95% CI: 1.29)</td>
</tr>
<tr>
<td>Pardi 2015</td>
<td>12-14</td>
<td>12</td>
<td>1.58 (95% CI: 1.29)</td>
</tr>
<tr>
<td>Deamer 2015</td>
<td>30-34</td>
<td>30</td>
<td>1.58 (95% CI: 1.29)</td>
</tr>
<tr>
<td>Koren 2016</td>
<td>23-14</td>
<td>14</td>
<td>1.58 (95% CI: 1.29)</td>
</tr>
<tr>
<td>Lemon 2017</td>
<td>26-11</td>
<td>11</td>
<td>1.58 (95% CI: 1.29)</td>
</tr>
<tr>
<td>Rank 2017</td>
<td>27-14</td>
<td>14</td>
<td>1.58 (95% CI: 1.29)</td>
</tr>
<tr>
<td>Total (n=271)</td>
<td>178</td>
<td>153</td>
<td>1.58 (95% CI: 1.29)</td>
</tr>
</tbody>
</table>

Virtual Grand Rounds

Budesonide Orodispersable Tablet as Induction Therapy in EoE

- Randomized phase 3 trial in 88 adult patients with active EoE
- 1 mg BOT twice daily (n = 59) vs placebo (n = 29) for 6 weeks
- Primary endpoint: rate of combined clinical-histologic remission at week 6
- Secondary endpoint: rate of histologic remission (<16 eos/mm²), <5 eos/hpf) at week 6

![Graph](https://via.placeholder.com/150)

Virtual Grand Rounds

American College of Gastroenterology
Budesonide Oral Suspension in EoE
Randomized Phase 3 Trial

- Randomized, double-blind, placebo-controlled trial of BOS in patients (11 to 55 years) with EoE and dysphagia
- 318 patients randomized 2:1 to 2 mg BOS or placebo twice daily for 12 weeks (BOS, n = 213; placebo, n = 105)
- Co-primary endpoints: histologic peak eosinophil count ≤ 6 eos/hpf and dysphagia symptom response after 12 weeks

<table>
<thead>
<tr>
<th>Histologic Response</th>
<th>Symptom Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>53.1%</td>
<td>57.8%</td>
</tr>
<tr>
<td>52.6%</td>
<td>39.1%</td>
</tr>
</tbody>
</table>

All APT-1011 dosing regimens showed statistically significant responder rates compared to placebo at Week 12

Choosing an Initial EoE Therapy

<table>
<thead>
<tr>
<th>PPI</th>
<th>Steroids</th>
<th>Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>30-50%</td>
<td>50-90%</td>
</tr>
<tr>
<td>Administration</td>
<td>Easy</td>
<td>Cumbersome (use of inhaled steroids)</td>
</tr>
<tr>
<td>Safety</td>
<td>High (long-term evaluation)</td>
<td>High (long-term evaluation)</td>
</tr>
<tr>
<td>Cost</td>
<td>Very low</td>
<td>Variable (insurance coverage)</td>
</tr>
</tbody>
</table>

Importance of shared decision making in selection of initial therapy for an individual patient

- Loss efficacy with prolonged use
- Loss efficacy in subset with prolonged use
- Repeated endoscopies; long-term adherence
New Therapeutic Options for Eosinophilic Gastrointestinal Disease

- What's wrong with symptom-based management in EoE?
- What's new with the "old" therapeutic options for EoE?
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Case Presentation
A 48-year-old woman with asthma, allergic rhinitis and 20-year history of progressive dysphagia
Initial ER food impaction 10 years ago. Endoscopy demonstrated a high-grade stricture not traversed. Disimpaction complicated by severe chest pain with pneumomediastinum. Biopsies obtained showed 75 eos/hpf. She was started on fluticasone 880 mcg swallowed BID. A repeat EGD on Flovent showed a persistent high grade stricture requiring use of a pediatric endoscope. Savary dilation was performed to 36 Fr with severe chest pain requiring hospitalization. Biopsies showed 65 eos/hpf.

2020 AGA/JTF Allergy/Immunology Guidelines: Management of EoE

Biologic Therapies: Anti-IgE
Recommendation: In patients with EoE the AGA/JTF suggests against the use of anti-IgE therapy (conditional recommendation; very low-quality evidence)

Biologic Therapies: Anti-IL-5
Recommendation: In patients with EoE the AGA/JTF recommends to use anti-IL-5 therapy only in the context of a clinical trial (no recommendation; knowledge gap).

Biologic Therapies: Anti-IL-13
Recommendation: In patients with EoE the AGA/JTF recommends to use anti-IL-13 or anti-IL-4 receptor alpha therapy only in the context of a clinical trial (no recommendation; knowledge gap).

Misc Therapies: Montelukast, Cromolyn, Immunomodulator, Anti-TNF
Recommendation: In patients with EoE the AGA/JTF suggest using montelukast, cromolyn sodium, immunomodulators, and anti-TNF only in the context of a clinical trial (no recommendation; knowledge gap).

American College of Gastroenterology
Novel Targeted Therapeutics in EoE

Anti-IL-5 Therapy for EoE
Histologic efficacy in randomized controlled trials

RPC4046: Anti-IL-13 Antibody
- Recombinant, humanised monoclonal (IgG1x) antibody, highly selective for IL-13
- Inhibits binding of IL-13 to the IL-13Ra1 and IL-13Ra2 receptors
- Administered as a weekly subcutaneous injection
RPC4046 Anti-IL-13 mAb reduced eosinophilic inflammation
Randomized, double blind, placebo-controlled trial; 99 patients; ages 18-65
16-week treatment: RPC4046 (SC) 180 mg or 360 mg versus placebo
Primary Endpoint: Change in mean esophageal eosinophil count

Secondary Endpoint: Mean Change in Symptom Score
(Daily Symptom Diary)

RPC4046 Open Label Extension Study

- OLE Objective: To characterize the long-term effects of RPC4046 in patients with symptomatic EoE on clinical symptoms, endoscopic scores, esophageal histologic findings, and safety for up to 52 weeks

Main Study
- 16 weeks treatment prior to OLE entry (N=99)

OLE Entry (N=86)
≥ 80% study drug compliance no clinically significant AEs
Dupilumab EoE Phase 2 Trial
Anti-IL-4 receptor α mAb inhibits signaling of IL-4 and IL-13

- Phase 2, multicenter, double-blind, randomized, placebo-controlled study in patients with active EoE

Randomization (1:1) N = 47

- Dupilumab SC 300 mg every week with 600 mg loading dose n = 23
- Placebo n = 24

Screening period (1–35 days)
12-week treatment period
16-week follow-up period

PLACEBO

Week 10

Week 12

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

Symptoms
Pathology
Endoscopy
Exploratory Endpoint
Dupilumab significantly improved esophageal distensibility plateau at Week 12

A Phase 3, Randomized, 3-Part Study to Investigate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients With Eosinophilic Esophagitis: Results From Part A

Evan S. Dellon, MD1, Marc E. Rothenberg, MD, PhD2, Margaret H. Collins, MD2, Biao Hirano, MD3, Minna Chehade, MD, MPH4, Albert J. Bredenoord, MD, PhD5, Alfredo J. Lucendo, MD, PhD6, Jonathan M. Sangen, MD, PhD2, Qing Zhou, MD, PhD4, Jennifer D. Hamilton, PhD5, Bethany Balsey, PhD4, Isabelle Guiffrida, PhD7, Siddhesh Kamat, MD, Leda Mannett, MD, Maureen Rusili, MD, MD8, Elisabetta Mancini, MD2, Solarte Aguirre, MD7, Niki Amrani, MD, Allan Radao, MD, MD8, Brad Shumel, MD9, Jennifer Maloney, MD8*, 

1University of North Carolina School of Medicine, Chapel Hill, NC, USA; 2Cincinnati Children’s Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, OH, USA; 3Northwestern University Feinberg School of Medicine, Chicago, IL, USA; 4Mount Sinai Center for Eosinophilic Disorders, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 5Amsterdam University Medical Center, Amsterdam, Netherlands; 6Children’s Hospital of Philadelphia, PA, USA; 7Mount Sinai Beth Israel, New York, NY, USA; 8Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; 9Sanofi, Bridgewater, NJ, USA

*Co-last authors

Co-primary endpoints: Dupilumab significantly reduced dysphagia and intraepithelial eosinophil counts at Week 24 (n=81)

Proportion of patients achieving peak esophageal intraepithelial eosinophil counts of ≤6 eos/hpf at Week 24

Responders (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dupilumab 300 mg qw</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Responders</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Number of responders (%</td>
<td>2 (5.1)</td>
<td>25 (59.5)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>39</td>
<td>42</td>
</tr>
</tbody>
</table>

**P** < 0.001
New Therapeutic Options for Eosinophilic Gastrointestinal Disease

- What’s wrong with symptom-based management in EoE?
- What’s new with the “old” therapeutic options for EoE?
- How do we manage refractory EoE?
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Therapeutic Choices for Eosinophilic Gastroenteritis

Medications:
- Systemic corticosteroids
- Proton pump inhibition
- Swallowed topical corticosteroids (budesonide)
- Antihistamine (ketotifen)
- Cromolyn sodium
- Immunomodulators (azathioprine)
- Omalizumab (Anti-IgE) (Foroughi et al. J Allergy Clin Immunol 2007;120:594-601)
- Mepolizumab (Anti-IL-5) (Prussin J Allergy Clin Immunol 2013; 11 abstract)
- Vedolizumab (Anti-α4β7 integrin)

Diet therapy
**Prospective Study of Elemental diet In Eosinophilic gastroenteritis Nutrition Trial (ELEMENT)**

15 adults (18-65 years) with histologically active EG/EGE (≥ 30 eos/hpf) in stomach and/or duodenum

- GI symptoms ≤ 1 month prior to enrollment
- Treated with elemental diet for 6 weeks

Primary endpoint: % of participants with complete histologic remission at end of treatment

**Histologic Improvement Post-Diet**


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**Benralizumab for PDGFRA-Negative Hypereosinophilic Syndrome**

Randomized, double-blind, placebo-controlled, phase 2 trial

20 patients with HES; Primary endpoint ≥50% reduction in peripheral eosinophil count achieved (90% active vs 30% placebo)

Gastrointestinal mucosal biopsies < 1 eos/hpf in 7 patients with GI involvement during OLE


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**Anti-Siglec-8 Antibody for Eosinophilic Gastritis and Duodenitis**

- Randomized, double-blind, placebo-controlled trial
- 65 adults with moderately severe UGI symptoms and active histology (gastric ≥30 eos/hpf in 5 hpf; duodenal ≥30 eos/hpf in 3 hpf)
- Anti-Siglec-8 mAb at 2 doses (1 mg/kg, 3 mg/kg) vs placebo
- 4 monthly doses with endpoints assessed 2 weeks after last dose

Anti-Siglec-8 Antibody for Eosinophilic Gastritis and Duodenitis: Primary Endpoint: Histologic Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Intention to Treat Analysis</th>
<th>Post Hoc Analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>High (n=30)</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>Low (n=30)</td>
<td></td>
</tr>
<tr>
<td>Change in Histologic Score (mean - SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilic</td>
<td>-0.12 (0.49)</td>
<td>0.03</td>
</tr>
<tr>
<td>Eosinophilic</td>
<td>-0.12 (0.76)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>-0.12 (0.60)</td>
<td>0.03</td>
</tr>
<tr>
<td>P-value</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

Anti-Siglec-8 Antibody for Eosinophilic Gastritis and Duodenitis: Primary Endpoint: Histologic Efficacy

Secondary Endpoint: Symptom Efficacy

Pharmaceutical pipeline for eosinophilic GI disease in 2020

More products moving forward than in past decade

American College of Gastroenterology
Why consider biologic therapy?

- Corticosteroid-refractory patients
- Avoid possible long-term adverse effects of corticosteroids
- Concept of therapy targeting specific allergic pathways
- Systemic treatment of multiple forms of atopy
- Potential benefits for esophageal remodeling as well as inflammation
- Potential benefits of intermittent rather than daily therapy

Novel Therapeutics on the Horizon for EGID

- Therapeutic goals of EoE therapy include symptoms, pathology, and remodeling consequences
- Regulatory approval of formulations of swallowed topical corticosteroids optimized for esophageal delivery will improve the management of EoE
- Emerging data on biologic therapies for EoE and EGE are promising

Questions?

Speaker:
Ikuo Hirano, MD, FACG

Moderator:
Christine Y. Hachem, MD, FACG