2022 ACG / FGS ANNUAL SPRING SYMPOSIUM
MARCH 11-13, 2022 | In-Person
HYATT REGENCY COCONUT POINT • NAPLES, FLORIDA

COURSE DIRECTORS:
Tolga Erim, DO and Joel E. Richter, MD, MACG

2022 ACG / LGS REGIONAL POSTGRADUATE COURSE
MARCH 18-20, 2022 | In-Person
HILTON NEW ORLEANS RIVERSIDE • NEW ORLEANS, LOUISIANA

COURSE DIRECTORS:
James D. Morris, MD, FACG and Eric P. Trawick, MD
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, 2022** 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, 2023** 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 7
Update: Prognostic Models in PSC-How Best to Inform our Patients
Mark W. Russo, MD, MPH, FACG
February 17, 2022 at Noon Eastern and 8pm Eastern!

Week 8
Current and Emerging Options for the Diagnosis and Management of EoE
Kishore Iyer, MBBS
February 24, 2022 at Noon Eastern and 8pm Eastern!

Visit gi.org/ACGVGR to Register

Disclosures:
Speaker:
Jennifer L. Horsley-Silva, MD
Regeneron, Allakos, Celgene - Clinical Trial Site

Moderator:
Diana L. Snyder, MD
Celgene. Clinical Trial Site

*All of the relevant financial relationships listed for these individuals have been mitigated

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS
• Nothing to disclose
• No FDA approved pharmacologic treatment for EoE to date
• All medications discussed are off-label use
CURRENT AND EMERGING OPTIONS FOR THE DIAGNOSIS AND MANAGEMENT OF EOSINOPHILIC ESOPHAGITIS

Jennifer L. Horsley-Silva, MD
Consultant, Division of GI and Hepatology
Assistant Professor of Medicine, College of Medicine
Mayo Clinic, Scottsdale, Arizona

LEARNING OBJECTIVES

- Examine how EoE is diagnosed and differentiate current treatment therapies including pharmacologic options, dietary practices, and esophageal dilation
- Discuss emerging diagnostic tools and treatment options
EOSINOPHILIC ESOPHAGITIS (EOE)

- First described
  - In early 1990’s - several case series
  - 2000’s therapies started to establish
  - ICD-9 classification in 2008

- Emerging as leading cause of esophageal morbidity
- Active area of research
- **Diagnostic tools and treatment options are rapidly evolving**

DIAGNOSIS

Clinicopathologic disorder

- Symptoms of esophageal dysfunction
- Eosinophil-predominant inflammation
  - ≥ 15 eos per high-power field
- Mucosal eosinophilia isolated to the esophagus
- Exclusion of secondary causes

EGD with biopsies
Evaluate for other contributing cause for esophageal eosinophilia

EoE

DIAGNOSIS

Symptoms

- Adults:
  - Dysphagia, food impaction, heartburn, chest pain
  - Always asked about diet behaviors

- Children:
  - Feeding intolerance, failure to thrive, regurgitation/reflux, abdominal pain, nausea, vomiting


DIAGNOSIS

Diet Behaviors

- Do you need liquids to eat a meal?
- Do you cut or puree your foods?
- Are you a slow eater? Do you chew excessively?
- Do you turn away foods or avoid pills?
- Do you use condiments to lubricate your food?
- Do you avoid social situations for fear of impaction or avoid eating in social settings?
DIAGNOSIS

- EGD with esophageal biopsy is still the necessary diagnostic test
- Biopsies from at least two different locations
  - Proximal and distal halves of the esophagus
  - At least 6 biopsies
- Endoscopic findings can also suggest the diagnosis
- EoE Endoscopic Reference Score (EREF)
  - Allows for consistency in description and standardized reporting

DIAGNOSIS

EDEMA

DIAGNOSIS

RINGS
DIAGNOSIS

- ≥ 15 eosinophils per high power field approaches 100% sensitivity and 96% specificity for EoE

Eosinophil microabscesses
Eosinophil degranulation
Superficial eosinophils

Courtesy of Dr. Lam-Himlin
DIAGNOSIS – EMERGING OPTIONS

Tissue sampling
• Unsedated transnasal endoscopy
  • Used more frequently at children centers
• Cytology sponge
  • FDA approved
  • 75% sensitivity, 86% specificity
• String test - adherent luminal secretions

Complementary studies
• Model to predict lamina propria fibrosis
• Esophagram
  • Double contrast with barium tablet
• Functional lumen imaging probe topography
  • High resolution impedance planimetry during volume-controlled distention
  • Assesses caliber and distensibility

Pathology alternatives
• Mucosal impedance
• Biomarkers

PATHOPHYSIOLOGY

Airborne allergens
Food allergens
Acute allergic inflammation

Mast cells produce TGF-β
Remodeling with deposition of collagen and fibrosis

Type 2 helper T cells
cause an inflammatory response from allergen trigger

Eosinophils release granule proteins, causing cytotoxic damage, disrupting the mucosal barrier and releasing profibrotic mediators

Cytokines IL-5, IL-13 stimulate esophageal epithelium to produce eotaxin-3

American College of Gastroenterology
TREATMENT

• Goal
  • Improvement in symptoms and quality of life
  • Maximize nutrition
  • Prevent complications related to remodeling and fibrosis
    • Food impaction, strictures, perforation
• Treatment endpoints in the literature are variable
  • Symptoms can be nonspecific and minimized by compensatory
dietary and lifestyle modifications
  • Histology and symptom discordance
  • Differing terms for upper limit of eosinophils/high power field

TREATMENT

• Treat to Target Approach
  • Symptoms
    • Resolution of dysphagia
    • Resolution of food avoidance
  • Histology
    • Resolution of esophageal eosinophilic inflammation
  • Endoscopic activity
    • Improvement in inflammatory features and strictures
    • Decrease in EREFS
    • Diameter >13-15 mm
TREATMENT

Patient with confirmed EoE
Consider first line therapies

PPI therapy
Swallowed topic steroids
Elimination diet

No remission
Histologic remission with persistent symptoms
Clinic and histologic remission

Switch between first line therapies above
Strictures/narrow caliber esophagus

No remission
Endoscopic dilation

Consider other agents and clinical trials
Long-term treatment with an effective anti-inflammatory drug or diet

Rule out other conditions unrelated to esophageal inflammation
Reevaluation of initial diagnosis

Redrawn from: Lucendo et al. United European Gastroenterol J, 2017

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Redrawn from: Lucendo et al. United European Gastroenterol J, 2017
TREATMENT

Current
• Proton pump inhibitors
• Swallowed topical corticosteroids
• Diet elimination
• Esophageal dilation

Emerging
• Novel corticosteroid formulations
• Biologics
• Leukotriene antagonists
• Mast cell stabilizers
• Immunomodulators
• Small molecules

In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using proton pump inhibition over no treatment (Conditional recommendation, very low-quality evidence).

Certainty in evidence rated down for inconsistency ($I^2 = 81\%$) and effect estimate was very low.
TREATMENT – PROTON PUMP INHIBITORS

• Any of the agents can be effective when used at ‘high daily dose’
  - Nonsignificant trend to higher histologic response when administered twice a day, compared to daily administration

• Overall unweighted histology response rate in observational studies (<15 eos/hpf) 42% in AGA JTF guidelines

• Various studies have shown 40-50% response rate

• Effectiveness, widespread availability, ease of administration, and safety profile makes this a popular first line treatment


PPIs Potential Mechanisms

- **Anti-inflammatory Effects**
  - Influence vacuolar H+ ATPases on eosinophils
  - Inhibit CK11b and CD18 expression in neutrophils
  - Inhibit expression of intracellular adhesion molecule-1 and vascular cell adhesion molecule-1
  - Block cytokine-stimulated eotaxin-3 secretion
  - Re-establishes basal progenitor cells

- **Gastric Acid-inhibiting Effects**
  - Reduce gastric acid secretion
  - Restore mucosal integrity / correct mucosal permeability
  - Influence gut microbiota

In patients with EoE, the AGA/JTF recommends topical glucocorticosteroids over no treatment (strong recommendation, moderate quality evidence).

Certainty in evidence rated down for inconsistency ($I^2$ 78%) that may be related to varying steroid dosing/delivery system, inclusion criteria, methodology to determine eosinophil density.

Forest plot for not achieving histologic remission

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Steroids Events</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td></td>
<td></td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Alexander 2012</td>
<td>4</td>
<td>21</td>
<td>14</td>
<td>21</td>
<td>9.6%</td>
<td>0.29 (0.11, 0.73)</td>
</tr>
<tr>
<td>Bata 2014</td>
<td>10</td>
<td>28</td>
<td>13</td>
<td>14</td>
<td>14.9%</td>
<td>0.39 (0.23, 0.65)</td>
</tr>
<tr>
<td>Debon 2017</td>
<td>32</td>
<td>51</td>
<td>41</td>
<td>42</td>
<td>19.0%</td>
<td>0.64 (0.52, 0.80)</td>
</tr>
<tr>
<td>Dohi 2010</td>
<td>2</td>
<td>15</td>
<td>16</td>
<td>16</td>
<td>7.5%</td>
<td>0.16 (0.05, 0.50)</td>
</tr>
<tr>
<td>Gupta 2015</td>
<td>30</td>
<td>60</td>
<td>19</td>
<td>21</td>
<td>18.2%</td>
<td>0.55 (0.41, 0.74)</td>
</tr>
<tr>
<td>Konkoff 2006</td>
<td>11</td>
<td>21</td>
<td>14</td>
<td>15</td>
<td>16.2%</td>
<td>0.56 (0.37, 0.86)</td>
</tr>
<tr>
<td>Mehlke 2016</td>
<td>1</td>
<td>57</td>
<td>13</td>
<td>19</td>
<td>3.2%</td>
<td>0.02 (0.00, 0.18)</td>
</tr>
<tr>
<td>Straumann 2010</td>
<td>5</td>
<td>18</td>
<td>16</td>
<td>18</td>
<td>11.5%</td>
<td>0.31 (0.15, 0.67)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>271</td>
<td>166</td>
<td>100</td>
<td></td>
<td>0.39 (0.26, 0.58)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>95</td>
<td>146</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


TREATMENT – TOPICAL STEROIDS

- 8 randomized controlled trials including 437 patients showed overall unweighted histology response rate (<15 eos/hpf) 65% in AGA JTF guidelines
- In general, on doses studied, response rate is around 65-70%
- Similar histologic efficacy for fluticasone 880 mcg BID MDI (64%) vs oral viscous budesonide 1 mg BID (71%)
- Side effects of candidiasis
- Potential long-term systemic adverse effects being studied
  - Adrenal insufficiency, growth suppression, osteoporosis

TREATMENT – TOPICAL STEROIDS

• Considered first line treatment option
• Mounting evidence that these agents are safe and well tolerated
• Swallowed topical glucocorticosteroids recommended over no treatment (strong recommendation, moderate quality of evidence)
• Reduction in need for dilation

Hirano et al. Gastro 2020; Rank et al. Gastro 2020

TREATMENT – TOPICAL STEROIDS

• Oral aerosolized fluticasone propionate
  • Fluticasone inhaler (220 mcg/puff)
    • Patient puffs into mouth during breath hold, then swallows
    • 880 mcg BID

• Oral viscous budesonide /fluticasone (compounded)
  • Liquid respules
    • Mixed with sucralose/Splenda
    • 1-2 mg BID
  • Compounded powder
    • Mixed with chocolate syrup or honey
TREATMENT – TOPICAL STEROIDS

Budesonide versus Fluticasone

Overall response: 68% (0.50-0.82)

Overall response: 77% (0.63-0.87)
TREATMENT – TOPICAL STEROIDS

Budesonide versus Fluticasone

- Maintenance dosing still needs to be determined
- Minimum dose to maintain remission unknown
- In initial responders, loss of treatment response was associated with steroid dose reduction
  - 0.25mg BID oral suspension budesonide
  - 1 year data with 36% in histologic remission
  - 5 year data with 16% in complete histologic remission

TREATMENT – TOPICAL STEROIDS

• Key is correct deposition on the epithelial surface layer
• Ease of administration
  • Budesonide effervescent tablet
    • Approved in Europe, Canada, Australia
  • Budesonide oral suspension
    • Recent phase 3 results
  • Fluticasone dissolvable tablet
    • Phase 1b/2a results


TREATMENT – DIET

• Options include:
  • Elemental Diet (90.8%)
  • Allergy Testing-Directed Diet (45.5%)
  • Empiric Elimination Diet (SFED 72.1%)

Arias A et al. Gastro 2014
TREATMENT – DIET

- Cow’s Milk (65%)
- Wheat (27%)
- Egg (26%)
- Soy (15%)
- Nuts
- Fish

> Computer-based simulation based on trigger prevalence – most efficient model

> Long duration of remission can be achieved if specific trigger food(s) avoided


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TREATMENT – DIET

• High drop out rate before maintenance phase
  - Despite partnering with dietitian
• Most that gave reasons for drop out preferred other treatment options
• Younger adults were more likely to decline after visiting with dietitian

USE your DIETITIAN
• How to read food labels and terminology
• Hidden allergens
• Suitable food replacements
• Ensure nutritional adequacy
• Access to resources
TREATMENT – DILATION

- What about patients with severe rings, focal strictures, narrow-caliber esophagus?
- Dilation can be performed safely
  - Perforation risk up to <1%
- Conservative approach with small increases in diameter
- Balloons or bougies are safe
- Multiple sessions
- Goal 15 mm
- Does not impact eosinophil burden
- Effective therapy with substantial duration


TREATMENT – DILATION

- Dilation does not impact eosinophil burden and does not alter the pathophysiology of disease
  - Effective therapy with substantial duration

<table>
<thead>
<tr>
<th>Author (year published)</th>
<th>Percentage having improvement after Dilation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croese (2003)</td>
<td>94 (71 -100)</td>
</tr>
<tr>
<td>Potter (2004)</td>
<td>54 (25-81)</td>
</tr>
<tr>
<td>Pasha (2007)</td>
<td>85 (55-98)</td>
</tr>
<tr>
<td>Bohm (2010)</td>
<td>89 (52-100)</td>
</tr>
<tr>
<td>Dellon (2010)</td>
<td>83 (63-95)</td>
</tr>
<tr>
<td>Schoepfer (2010)</td>
<td>93 (81-99)</td>
</tr>
<tr>
<td>Enns (2010)</td>
<td>17 (2-48)</td>
</tr>
<tr>
<td>Overall (I²=86%, P=0.000)</td>
<td>75 (57-93)</td>
</tr>
</tbody>
</table>

TREATMENT – EMERGING OPTIONS

Current
• Proton pump inhibitors
• Swallowed topical corticosteroids
• Diet elimination
• Esophageal dilation

Emerging
• Novel corticosteroid formulations
• Biologics
• Leukotriene antagonists
• Mast cell stabilizers
• Immunomodulators
• Small molecules

TOPICAL STEROIDS – BUDESONIDE ORAL SUSPENSION

• Phase 3 data from ACG 2019:

- Histologic response
- Symptom reduction

Hirano I et al. Am J Gastro, 2019
## TOPICAL STEROIDS – FLUTICASONE DISSOLVABLE TABLET

- Phase 2b RCT – 4 doses vs placebo (n = 103)

### Histologic response (1°)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean % change EREFS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-17.3</td>
<td></td>
</tr>
<tr>
<td>1.5 mg HS</td>
<td>-45.3</td>
<td>p=0.001</td>
</tr>
<tr>
<td>3 mg HS</td>
<td>-62.3</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>1.5 mg BID</td>
<td>-58.7</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>3 mg BID</td>
<td>-48.9</td>
<td></td>
</tr>
</tbody>
</table>

### Endoscopic response (2°)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean % change EEsAI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1.5 mg HS</td>
<td>-9.6</td>
<td>p=0.071</td>
</tr>
<tr>
<td>3 mg HS</td>
<td>-20.4</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>1.5 mg BID</td>
<td>-22.6</td>
<td>p=0.036</td>
</tr>
<tr>
<td>3 mg BID</td>
<td>-22.7</td>
<td></td>
</tr>
</tbody>
</table>

### Symptomatic response (2°)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean % change EEsAI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-17.3</td>
<td></td>
</tr>
<tr>
<td>1.5 mg HS</td>
<td>-45.3</td>
<td>p=0.001</td>
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</tr>
<tr>
<td>3 mg BID</td>
<td>-48.9</td>
<td></td>
</tr>
</tbody>
</table>

### Histologic response (1°)

- Histologic remission (<16 eos/mm²)
  - Budesonide: 93.2%
  - Placebo: 0%
  - *p<0.0001

- Clinical remission (sx < 2 of 10 pt scale)
  - Placebo: 57.6%
  - *p<0.0001

- Clinical remission (EEsAI <20)
  - Budesonide: 59.3%
  - Placebo: 13.8%
  - *p<0.0001

- No EdE endoscopic signs
  - Budesonide: 61%
  - Placebo: 6.9%
  - *p<0.0001

- Change in peak eos/mm²: -226 in budesonide; -4 in placebo (p<0.0001)

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**References:**

- Dellon et al. UEGW, 2019; Phase 1b/2a data: Hirano et al. APT, 2020
- Lucendo et al. Gastro, 2019
- American College of Gastroenterology
TOPICAL STEROIDS – BUDESONIDE ORODISPERSIBLE TABLET

- Phase 3 RCT in Europe (1:1:1) 1 mg BID (n=68) : 0.5 mg BID (n=68) : placebo (n=68)

- Both groups highly superior to placebo (p<0.0001)

TREATMENT - BIOLOGICS

- Dupilumab (Dupixent)
  - Human monoclonal ab against IL-4 receptor alpha
  - FDA approved for atopic dermatitis, asthma, chronic sinusitis with nasal polyposis
  - Initial Phase 3 data 83% histologic remission at 12 weeks

- Benralizumab (Fasenra)
  - Monoclonal ab against IL-5 receptor alpha
  - FDA approved for eosinophilic asthma
  - Phase 2 in hypereosinophilic syndrome with GI involvement showed elimination of eosinophils in GI tract
  - Phase 3 ongoing
TREATMENT - BIOLOGICS

• CC-93538
  • Human monoclonal ab against IL-13
  • Phase 2 with 50% histologic remission at 16 weeks, symptoms and endoscopic severity improved
  • Maintenance of response to 52 weeks
  • Phase 3 ongoing

• Lirentelimab
  • Monoclonal ab to sialic acid-binding immunoglobulin-like lectin 8 (Siglec 8) on eosinophils
  • Induces apoptosis in eosinophils and inhibits activation of mast cells
  • Phase 3 ongoing


TREATMENT - BIOLOGICS

• Mepolizumab; Reslizumab
  • Human monoclonal ab against IL-5
  • FDA approved for eosinophilic asthma
  • Multiple initial trials showing decreased eosinophil count in the esophagus
  • Phase 2 ongoing
**PATHOPHYSIOLOGY**

- **Airborne allergens**
- **Food allergens**
- **Acute allergic inflammation**

**Mast cells** produce TGF-β, remodeling with deposition of collagen and fibrosis.

**Eosinophils** release granule proteins, causing parenchymal damage, disrupting the mucosal barrier and releasing probiotic mediators.

- **anti-Siglec-8 (Lirentelimab)**
- **anti-IL-13 (CC-93538) (Mepolizumab)**
- **anti-IL-5α (Benralizumab)**
- **anti-IL-4α (Dupilumab)**

**MULTIDISCIPLINARY APPROACH**

**American College of Gastroenterology**
TAKE HOME POINTS

• Diagnosis requires symptoms, esophageal eosinophilia, and exclusion of other causes
• Current first line treatments include PPI, topical steroid, and dietary elimination
• Dilation takes caution, but is safe and likely underutilized
• Long-term disease requiring maintenance and monitoring
• Cost-effective care should be patient-centric with shared decision-making
  • Esophageal specific topical steroid formulations are coming
  • Dietary therapy may focus more on efficiency
  • Future biologics

Questions?

Speaker:
Jennifer L. Horsley-Silva, MD

Moderator:
Diana L. Snyder, MD
Adapted from Dr. Jeffrey Alexander

### PPI

- **Pros**
  - Easy to take
  - Relatively inexpensive
  - Many of patients also have GERD
- **Cons**
  - PPI risks
  - Lower response rate

### Steroids

- **Pros**
  - Unlimited diet
  - Most patients respond
- **Cons**
  - Expensive
  - No commercially available preparation
  - Potential risks

### Diet

- **Pros**
  - No long term risk
  - Relatively inexpensive
- **Cons**
  - Cost, risks, inconvenience of evaluation period
  - Long term dietary restriction

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