Welcome to the Virtual Grand Rounds Waiting Room – The educational activity will begin promptly at 12 Noon Eastern.

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Grant System Opens: September 8, 2020
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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.
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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.

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Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.
ACG Virtual Grand Rounds
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Week 26: Current and Emerging Concepts in Irritable Bowel Syndrome
Brooks D. Cash, MD, FACG
*September 17, 2020 at Noon EDT*

Week 27: Making the Case for Screening 45-Year-Old Adults for CRC
Joseph C. Anderson, MD, MHCDS, FACG
*September 24, 2020 at Noon EDT*

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Disclosures:

Gary W. Falk, MD, MS, FACG
Consultant: Adare, Allakos, Lucid, Shire/Takeda
Research Support: Adare, Allakos, Lucid, Regeneron, Shire/Takeda

Joseph G. Cheatham, MD, FACG
No conflicts of interest.

Management of EoE With Topical Steroids: The When and How of Long Term Management

Gary W. Falk, MD, MS, FACG
Professor of Medicine
Division of Gastroenterology
University of Pennsylvania Perelman School of Medicine
Learning Objectives

- Where do topical steroids fit in the management of EoE?
- What is the efficacy of topical steroids?
- What is the status of new topical steroids?
- What is the rationale for chronic therapy?
- What are the data for chronic therapy?
- What are risks of chronic therapy?

Case

- 20 yr. old Penn varsity swimmer with EoE dating back to 1st grade
- EGD in 2017 with strictures, furrows, rings, exudates and adult scope could not pass
- Only therapy at initial visit in 2017 was bid PPI
EGD 10/17 On Budesonide 1 mg bid

Pathology
- 35 eosinophils/HPF,
- No superficial layering of eosinophils
- Rare eosinophilic microabscesses
- Basal cell hyperplasia and subepithelial lamina propria fibrosis

Emergency EGD 2/19 For Food Bolus Impaction After Noncompliance for 2 Years
EGD 4/19 Now On Budesonide 1 mg BID
After 2 Years Noncompliance

Pathology
• 110 eosinophils/hpf
• Basal cell hyperplasia and subepithelial lamina propria fibrosis

Learning Objectives

• Where do topical steroids fit in the management of EoE?
  • What is the efficacy of topical steroids?
  • What is the status of new topical steroids?
  • What is the rationale for chronic therapy?
  • What are the data for chronic therapy?
  • What are risks of chronic therapy?
Eosinophilic Esophagitis Management Options

• Diet
• Drugs
  – PPI
  – *Topical steroids*
• Dilation
• New agents

Learning Objectives

• Where do topical steroids fit in the management of EoE?
• **What is the efficacy of topical steroids?**
  • What is the status of new topical steroids?
  • What is the rationale for chronic therapy?
  • What are the data for chronic therapy?
  • What are risks of chronic therapy?
8 Week RCT of Budesonide (1 mg BID) vs. Fluticasone (880 ug BID) For EoE


Topical Corticosteroid Therapy for EoE: AGA & Joint Task Force Guideline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Studies (All RCT)</th>
<th>Number of Patients</th>
<th>Overall Effect</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical steroids</td>
<td>8</td>
<td>437</td>
<td>65%</td>
<td>77%</td>
</tr>
</tbody>
</table>

Efficacy: < 15 eosinophils/hpf

Topical Corticosteroid Therapy for EoE: AGA & Joint Task Force Guideline

- Recommends topical steroids over no therapy
  - Strong recommendation
  - Moderate quality evidence
- Only treatment option in guideline with strong recommendation


Learning Objectives

- Where do topical steroids fit in the management of EoE?
- What is the efficacy of topical steroids?
- What is the status of new topical steroids?
- What is the rationale for chronic therapy?
- What are the data for chronic therapy?
- What are risks of chronic therapy?
New Topical Steroid Treatment Options for EoE

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Study Phase</th>
<th>Trial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shire/Takeda</td>
<td>Premixed budesonide slurry</td>
<td>3</td>
<td>Completed</td>
</tr>
<tr>
<td>Adare</td>
<td>Fluticasone orally disintegrating tablet</td>
<td>3</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Falk Pharma</td>
<td>Budesonide orally dispersible</td>
<td>Approved in Europe</td>
<td>Completed</td>
</tr>
</tbody>
</table>

Budesonide Oral Suspension for EoE

- Phase 2 RCT
  - Budesonide oral suspension 2 mg bid vs placebo
  X 12 weeks

- Endpoints
  - DSQ change from baseline
  - Histology: Eo count ≤ 6/hpf

RCT of Budesonide 2 mg BID Oral Suspension for EoE


6 Week RCT of Budesonide 1 mg BID Orodispersible Tablets in EoE: Combined Endpoint

Combined Endpoint:
- < 5 eos/hpf
- Dysphagia/odynophagia severity ≤ 2 for all 7 days prior to end of therapy

Response increased to 85% if treatment extended to 12 weeks

6 Week RCT of Budesonide 1 mg BID Orodispersible Tablets in EoE: Histologic Remission (< 5 eos/hpf)


Histologic remission: 93% vs 0%

RCT of Fluticasone Propionate Orally Disintegrating Tablets vs. Placebo for EoE

Learning Objectives

• Where do topical steroids fit in the management of EoE?
• What is the efficacy of topical steroids?
• What is the status of new topical steroids?
• **What is the rationale for chronic therapy?**
• What are the data for chronic therapy?
• What are risks of chronic therapy?

Natural History of Untreated EoE in 30 Adults Followed Up to 11.5 Years

Natural History of Untreated EoE in 30 Adults Followed Up to 11.5 Years

Subepithelial fibrosis increased in 6/7 patients where biopsies of lamina propria available


Decreased Distensibility in Pediatric EoE

Strictures in EoE vs. Diagnostic Delay


EoE Endoscopic Features At Diagnosis vs. Diagnostic Delay

Progression of EoE from Inflammation to Fibrosis


Time to Clinical Relapse After Cessation of Topical Steroids in Patients with Deep Remission

82% with clinical relapse off therapy at median of 22.4 weeks

Recurrence of EoE After RCT of Budesonide vs. Fluticasone

- 33/58 (57%) with symptom recurrence prior to 1 yr
- Median time to symptom recurrence 244 days
- For those with symptoms median time to recurrence 130 days
- No predictors of recurrence


Recurrence of EoE After RCT of Budesonide vs. Fluticasone: Poor Agreement Between Symptom Recurrence & Histologic Relapse

<table>
<thead>
<tr>
<th></th>
<th>Symptom recurrence (n = 33)</th>
<th>No symptom recurrence (n = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak overall eosinophil count, eos/hpf ± SD</td>
<td></td>
<td></td>
<td>.91</td>
</tr>
<tr>
<td>Eosinophil count ≥ 15 eos/hpf, n (%)</td>
<td>54.1 ± 40.1</td>
<td>52.6 ± 53.5</td>
<td></td>
</tr>
<tr>
<td>Eosinophil count ≥ 5 eos/hpf, n (%)</td>
<td>22 (81)</td>
<td>17 (74)</td>
<td>.52</td>
</tr>
<tr>
<td>Eosinophil count ≥ 1 eos/hpf, n (%)</td>
<td>25 (93)</td>
<td>21 (91)</td>
<td>.87</td>
</tr>
<tr>
<td>78% with histologic relapse at symptom recurrence or 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recurrence of EoE After RCT of Budesonide vs. Fluticasone

• EREFs increased
• Esophageal caliber decreased during observation


Recurrence of EoE After RCT of Budesonide vs. Fluticasone: Key Points

• Recurrence [histologic and symptomatic] is rapid after induction of remission
• Recurrence is seen in vast majority of patients
• No predictors of recurrence
• Previously dilated strictures narrowed to pretreatment diameter

Rationale for Chronic Therapy

• Disease persists without treatment:
  – Natural history studies
  – Placebo arms of clinical trials
• Prolonged disease duration without treatment leads to fibrostenotic complications
• Disease activity recurs after cessation of therapy


Learning Objectives

• Where do topical steroids fit in the management of EoE?
• What is the efficacy of topical steroids?
• What is the status of new topical steroids?
• What is the rationale for chronic therapy?
• What are the data for chronic therapy?
• What are risks of chronic therapy?
Fluticasone Maintenance Therapy in Children


Long Term Steroid Therapy (0.25 mg bid) in EoE

- 229 patients in Swiss EoE database followed after induction of remission with 1 mg bid topical steroid
- Dose then reduced to 0.25 mg bid for maintenance
- Median FU 5 yrs. [IQR 3-7 yrs.]

Long Term Steroid Therapy (0.25 mg bid) in EoE


Long Term Steroid Therapy (0.25 mg bid) in EoE: Treatment Duration & Cumulative Dose

Efficacy of Budesonide Oral Suspension 24 Week Maintenance Therapy (2 mg QD) in EoE

- 42% of patients responding to double blind therapy maintained histologic response
- Response maintained in all who had dose escalation to 1.5-2 mg bid


Budesonide Orodispersible Tablets: 48 Week Maintenance of Remission in EoE

Remission: Symptom severity < 4 + < 15 eos/hpf

Budesonide Orodispersible Tablets for 48 Weeks in EoE: Time to Clinical Relapse


Swallowed Corticosteroids Reduce Risk for Long-Lasting Bolus Impactions in EoE: Swiss EoE Cohort Study

Control of Inflammation Decreases Need for Dilation

• UNC cohort study
• N=55 patients with dilation at baseline and subsequent endoscopy after topical steroid trial
• Responders: < 15 eos/hpf


<table>
<thead>
<tr>
<th></th>
<th>Nonresponders (N=28)</th>
<th>Responders (N=27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal diameter after dilation</td>
<td>15.8 ± 2.7</td>
<td>16.6 ± 2.1</td>
<td>0.19</td>
</tr>
<tr>
<td>Dilations needed after treatment</td>
<td>4.6 ± 4.6</td>
<td>1.6 ± 4.6</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Long-Term Therapy of EoE: Unanswered Questions

• Is fibrostentotic disease inevitable in all untreated patients?
• Is maintenance therapy necessary to avoid fibrosis?
• Is complete histologic remission needed to maintain remission?
• Is maintenance therapy durable?
• Is fibrosis reversible?
• Do age and disease duration impact response to therapy?
• What are risks of years of maintenance therapy?

Eosinophilic Esophagitis: Maintenance Therapy Candidates

• Narrow caliber esophagus
• Recurrent food impactions
• Strictures
• Rapid return of symptoms off therapy
• Prior spontaneous or dilation induced perforation
• Comorbid conditions increasing risk of endoscopy & dilation
• Travel to areas where food impaction causes increased risk

AGA & Joint Task Force Guideline: Maintenance Therapy

• For EoE patients in remission (< 15 eos/hpf) after short term topical steroids continuation of topical steroids **recommended over discontinuation**
  • Conditional recommendation
  • Very low quality evidence


AGA & Joint Task Force Guideline: Maintenance Therapy

• EoE patients in remission (< 15 eos/hpf) after short term topical steroids **can reasonably cease therapy** after initial remission obtained if:
  • High value placed on avoidance of long term topical steroids & possible adverse events
  • Lower value on prevention of potential long term complications
  • Clinical follow up maintained

AGA & Joint Task Force Guideline: Maintenance Therapy Caveats

- Lack of prospective natural history studies
- Paucity of studies on maintenance therapy
- Spontaneous disease remission reported but uncommon


Learning Objectives

- Where do topical steroids fit in the management of EoE?
- What is the efficacy of topical steroids?
- What is the status of new topical steroids?
- What is the rationale for chronic therapy?
- What are risks of chronic therapy?
Budesonide Orodispersible Tablets for 48 Week Maintenance of Remission in EoE: Adverse Events

- Candidiasis
  - BOT 0.5 mg bid-16.1%
  - BOT 1 mg bid-11.8%

- Mean AM cortisol no change in placebo or either treatment group
  - < 6.2 ug/dL in 4 BOT patients


Systematic Review: Adrenal Insufficiency Due to Topical Steroids in EoE

- 7 RCT of short term therapy
  - No difference vs placebo groups

- 10 observational studies
  - No change in pre vs post measures of adrenal function

Systematic Review: Adrenal Insufficiency Due to Topical Steroids in EoE

• Variables to consider
  – Duration of therapy
  – Concomitant steroid formulations for other indications
  – Measures of adrenal axis
    • High dose ACTH stimulation test optimal
    • Fasting AM cortisol reasonable surrogate


Systematic Review: Adrenal Insufficiency Due to Topical Steroids in EoE

• “At present available data do not support routine assessment of the adrenal axis in patients with EoE on topical corticosteroids”
• More attention to adrenal axis in patients on prolonged steroids for multiple conditions

Topical Corticosteroid Therapy for EoE: AGA & Joint Task Force Guideline

• No increased risk of AEs when compared to placebo in short term studies

• Scattered reports:
  – Adrenal suppression
  – Local fungal/viral infections


Topical Corticosteroid Therapy for EoE: AGA & Joint Task Force Guideline

• Same inhaled steroids considered safe for children & adults with asthma

• Routinely used in primary management of asthma

Summary

- EoE is a chronic disease associated with tissue remodeling
  - Stricture formation
  - Decreased esophageal distensibility
  - Dysphagia, food impaction & impaired QOL
- Topical steroids induce remission in 65-70% of patients
- A variety of esophageal specific steroid delivery systems under development
- Relapse is the norm after cessation of therapy
- Chronic topical steroids at appropriate dosing capable of maintenance of remission
- Chronic topical steroids leads to
  - Decreased food impactions
  - Decreased need for dilation
- Maintenance therapy appears to be safe to date
  - Be aware of other corticosteroid use

Remember Eosinophilic Esophagitis

Maintenance Therapy Candidates

- Narrow caliber esophagus
- Recurrent food impactions
- Strictures
- Rapid return of symptoms off therapy
- Prior spontaneous or dilation induced perforation
- Comorbid conditions increasing risk of endoscopy & dilation
- Travel to areas where food impaction causes increased risk

Summary

- Lack of FDA approved therapies remains a major unmet need
- Multiple compounds to treat EoE are in the pipeline
- Clinical trials remain hampered by endpoint problems
  - Endoscopy
  - Histology
  - PRO
  - Exclusion of most severe patients

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Questions?

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Joseph G. Cheatham, MD, FACG
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