What are the treatment endpoints for eosinophilic esophagitis?

Nicholas J. Shaheen, MD, MPH

Overview

• EoE defined
• Why do we treat EoE?
• What treatment outcomes should be used?
• Treatment: The 3 D’s – Drugs, Diet, Dilation
• Long term treatment?
EoE diagnostic criteria

- Symptoms related to esophageal dysfunction
- Eosinophil-predominant inflammation on esophageal biopsy, characteristically with $\geq 15$ eos/hpf
- Mucosal eosinophilia isolated to the esophagus and persists after a PPI trial
- Secondary causes of esophageal eosinophilia excluded

Histopathologic findings

Max 45 eos/hpf

Courtesy of Dr. John T. Woosley, UNC
Biopsy yield by diagnostic cut-point

Gonsalves et al, GIE, 2006; similar data in Shah et al, AJG, 2009

Why do we treat EoE?

• Improve symptoms
Why do we treat EoE?

• Improve symptoms
• Prevent complications

Why do we treat EoE?

• Improve symptoms
• Prevent complications
• Prevent progression
What treatment outcome?

EoE and treatment outcomes

Editorial

Therapeutic End Points in Eosinophilic Esophagitis: Is Elimination of Esophageal Eosinophils Enough?

Possible outcome measures
- Histology
- Symptoms
- Quality of life
- Complications
- Endoscopy
- Esophageal compliance
- Biomarkers

Hirano, CGH, 2012
Problems with outcomes

- Not well defined
- Not standardized in the literature
- Possibility of discordance
  - Symptoms improve but inflammation persists
    - Diet modification
    - Dilation
  - Inflammation improves but symptoms persist
    - Strictures
    - Infections

Solution? Validated outcomes!
EoE treatment options

Pharmacologic therapy

- Corticosteroids (systemic; topical)
- Leukotriene antagonists (montelukast)
- Mast cell stabilizers (cromolyn)
- Immunomodulators (6-MP; azathioprine)
- Biologics (anti-IL-5; anti-IL-13; anti-IgE; anti-TNF)
- Small molecules (CRTH2 antagonist)
- New directions

Dietary therapy

Endoscopic therapy (dilation)

No FDA-approved medications for EoE!

EoE treatment options

Pharmacologic therapy

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**Topical steroids – eosinophil counts**

<table>
<thead>
<tr>
<th>Year</th>
<th>Design</th>
<th>Subjects</th>
<th>Med</th>
<th>Rx Time</th>
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<tr>
<td>2006</td>
<td>RCT</td>
<td>36 children</td>
<td>FP 880/d</td>
<td>3 mos</td>
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<td>2008</td>
<td>RCT (open)</td>
<td>80 children</td>
<td>FP 440-880/d*</td>
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<td>RCT</td>
<td><strong>36 adults</strong></td>
<td>Bud 2mg/d**</td>
<td>15 days</td>
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<td>2010</td>
<td>RCT</td>
<td>24 children</td>
<td>Bud 1-2mg/d***</td>
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<td>2012</td>
<td>RCT</td>
<td><strong>42 adults</strong></td>
<td>FP 1760/d</td>
<td>6 wks</td>
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<td>2014</td>
<td>RCT</td>
<td>81 children</td>
<td>Bud 0.35 - 4mg/d***</td>
<td>12 wks</td>
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</table>

*Compared to prednisone; **Swallowed nebulized budesonide; ***oral viscous budesonide

**Corticosteroids in EoE - Recs**

Current recommendations:
- Fluticasone 220 μg inhaler, 4 puffs BID, or…
- Budesonide 1 mg BID mixed with a thickening agent
- Tips for most effective use:
  - for MDI, swallow medication during breath hold
  - NPO x 30-60 minutes after administration
  - 8 weeks of treatment followed by endoscopy

Unknowns: Best duration of therapy; best type of topical preparation; reasons for “steroid-refractory” cases; long term side effects
EoE treatment options

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Dietary therapy

Endoscopic therapy (dilation)

Anti-IL-13

Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis

Marc E. Rottemberg, MD, PhD,* Ting Wen, PhD,* Allison Greenberg, BA,‡* oral Alvarez, MD,* Benjamin Ever, MD,*‡ and Kayo Ishida, MD, PhD,* Karl Nadeau, MD, PhD,* Sergio Kaiser, PhD,* Thomas Peters, Dr rer nat,* Antonio Perez, MD, PhD,* Ivar Johnson, BA,* Jonathan P. Arm, MD,* Robert M. Striker, MD, FCCP, MAACP,* Ronald Saba, BA,* and Kukashi A. Gunawardana, MD, MRCP*†

Cincinnati, Ohio; Fairlawn, Va; Chicago, Ill; Stanford, Calif; Basel, Switzerland; Cambridge, Mass; and Harrow, United Kingdom

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EoE treatment options

Dietary therapy in EoE

- The best therapy?
- Rationale: food allergens may contribute to the pathogenesis of EoE
- Downsides:
  - reliability of detecting food allergy
  - difficulty with dietary compliance
- Three overall strategies:
  - elemental diet
  - six food elimination (“SFED”)
  - targeted elimination
Meta-analysis – diet therapy

Efficacy of Dietary Interventions for Inducing Histologic Remission in Patients With Eosinophilic Esophagitis: A Systematic Review and Meta-analysis
Angel Arias,1 Jesús González-Cervera,9 José M. Tenias,1 and Alfredo J. Lucendo5

Elemental: 91%
SFED: 72%
Targeted: 46%

Elemental diet - adults

Elemental Diet Induces Histologic Response in Adult Eosinophilic Esophagitis
Kathryn A. Peterson, MD, MPH, FACG, Kathryn R. Byrne, MD, Laura A. Simon, MD, Jun Yang, PhD, Kathleen K. Boynton, MD, John C. Fang, MD, Gerald J. Gehly, MD, Douglas S. Adler, MD, and Frederick actors, MD

• 29 patients enrolled, 11 could not adhere to the diet
• 13/18 (72%) with histologic response < 10 eos/hpf; mean eos decreased from 54 to 10
• Endoscopic findings (except for strictures) improved
• 6 subjects with food reintroduction – recurrent eosinophilia within 2-7 days

AJG, 2013
SFED - adults

Elimination Diet Effectively Treats Eosinophilic Esophagitis in Adults; Food Reintroduction Identifies Causative Factors

- 50 EoE pts empirically eliminated milk, soy, egg, wheat, nuts, seafood/shellfish x 6 wks
  - 64% had complete response (≤ 5 eos/hpf)
  - 94% had improved symptom scores
  - Reintroduction of foods (n = 20)
    - Median recurrence 3 days
    - Wheat (60%) and milk (50%) most common allergens
    - Skin prick testing identified only 13% of causal agents

Gastro, 2012

Less restrictive options? 4FED

Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study

- Eliminated dairy, wheat, eggs, legumes
  - 54% response rate (< 15 eos/hpf)
- Gonsalves et al – DDW 2013 #877
  - Eliminated dairy, wheat, egg, soy
  - 46% response rate (≤ 5 eos/hpf)
- Kagalwalla et al – DDW 2015 #114
  - 55 children eliminated dairy, wheat, egg, soy
  - 71% response rate (< 15 eos/hpf)

JACI, 2014; DDW, 2013; DDW 2015
Less restrictive options? 1FED

Some thoughts on diet therapy

• It works
• It can be hard for patients
• It is resource and time intensive
• Multi-disciplinary approach is key
• Ongoing questions:
  • Better testing to identify food allergies?
  • Best approach to adding back foods?
  • Less restrictive diets? (4FED; 2FED; 1FED)
Nicholas J. Shaheen, MD, MPH, FACG

### EoE treatment options

**Pharmacologic therapy**
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**Dietary therapy**

Endoscopic therapy (dilation)

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**Endoscopic therapy (dilation)**
Endoscopic therapy (dilation)

Dilation and complications?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n*</th>
<th>Perfs</th>
<th>Boerhaave’s (spontaneous)</th>
<th>Tears/rents</th>
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<td>13</td>
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<td>10 (77)</td>
<td>2 (15)</td>
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<td>Cohen</td>
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<td>36</td>
<td>3 (8)</td>
<td>1 (3)</td>
<td>7 (19)</td>
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(Multiple other case reports of esophageal perforation (both spontaneous and as a result of endoscopic intervention) in patients with EoE: Ligouri, World J Gastro, 2008; Lucendo, Endoscopy, 2007; Eisenbach, Endoscopy, 2006; Prasad, Dis Esoph, 2005; Riou, Ann Thorac Surg, 1996)

*number of dilations reported, with the exception of Kaplan where it is the number of EGDs
Less risk in the “modern” era

<table>
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<tr>
<th>Author</th>
<th>Year</th>
<th>n*</th>
<th>Perfs</th>
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* number of patients, rather than dilations reported; **prospective RCT

Dilation – patient perspective

Follow-up of 42 patients after dilation alone for EoE:

- Duration of improved dysphagia:
  - Post-EGD retrosternal pain in 74%
    - 36% slight; 21% moderate; 17% severe
  - Acceptability: all patients would have repeat dilation if needed (19% thought it was very cumbersome)

Schoepfer et al, Am J Gastro, 2010
Some thoughts on dilation

• No direct comparative data on technique
• Safety data published for both balloons and bougies
• Educate patients on post-procedural discomfort
• Cautious approach

Balloon - after 13.5mm

Balloon - after 15mm

Savary - after 12.8mm

Savary - after 14mm
Long term treatment?

Long term treatment

- EoE is chronic and (in some patients) progressive
- Symptoms, endoscopic findings, and eosinophilic inflammation tend to recur after treatment is stopped
- Maintenance/long term therapy should be considered:
  - Rapid symptom recurrence
  - Complications (strictures, food impaction, etc)
- Additional long-term safety data are needed
Summary algorithm

New EoE diagnosis
- Stricture present

Topical steroids or dietary elimination
- Response
  - Maintenance therapy
  - Assess compliance
  - Further diet restriction

- Non-response
  - Stricture present
  - Exclusion: infection and reconsider other causes of esophageal eosinophilia

Switch from steroids to diet or from diet to steroids
- Increase steroid dose or change formulation
- Consider second line agents or clinical trials

Dilation