Esophageal Function Testing: Effective Use in Practice

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Esophageal Function Tests: The Menu

- Reflux Monitoring (telemetry capsule, imp/pH)
- Manometry (HRM, traditional, Mano/MII)
- Barium Swallow (video with bolus)
- Nuclear Emptying
- MII impedance
Telemetry Capsule

- 48 or 96 hour monitoring
- Patient friendly
- Can be placed at EGD
- Reimbursement tricky

Prolonged pH (reflux) monitoring

- Allows investigation of:
  - the amount and timing of acid reflux
  - the correlation between acid reflux and symptoms
  - the effect of therapy on acid reflux
  - Non acid reflux (impedance)
Should pH (Reflux) Monitoring Be Performed Off or On Therapy?

- Low pre test probability of GERD at baseline/endoscopy not done
  - **OFF** Medication (7-10 days)
- GERD likely so need to assess efficacy of treatment/normal EGD
  - **ON** Medication (impedance/pH)

Katz PO et al Am J Gastroenterol 2013: March

Which technology

Combination of impedance and pH
my choice for ON therapy monitoring

Telemetry capsule choice for OFF
Evaluation of Esophageal Function

- Esophageal manometry for diagnosis of specific motility disorder (pressure)
- Assess bolus movement with barium and/or impedance
- Esophageal length caliber/solid upright transit with barium (manometry)

High Resolution Manometry

- Easier, faster, less catheter movement
- Allows for more extensive and more physiologic classification of motility/sphincters
- Color plots allow enhanced “picture” unless you are red/green color blind
- Catheter life short (200 studies)
- Interobserver agreement on reading better than line tracings
Case 1

- 38-year-old female with recent onset heartburn and dysphagia
- Occasional liquid regurgitation (non-acidic)
- Other medical conditions: mild allergies, BMI 24
- No prior surgery
- Treated by primary care provider with H2RAs and subsequently PPIs without benefit
- Occasional non-exertional chest pain
- Barium swallow “tertiary contractions” but normal esophageal emptying, no reflux or anatomical abnormality
- Endoscopy: normal appearance, esophageal biopsies negative for eosinophils
- Manometry: to be shown

Case 1: Esophageal manometry
Case 1: Esophageal pressure topography

- Esophageal Shortening
- Isobaric zone: 60 mmHg

Case 1

- Calcium channel blockers
- 5’ phosphodiesterase inhibitors
- Pneumatic dilation?
- Laparoscopic Heller myotomy
- Botox™ injection to LES
- Peroral Endoscopic Myotomy
Esophageal Pressure Topography

There is a lot of unrecognized achalasia out there!

Response Rates of Achalasia Treatments

83 Patients categorized by pressure topography subtype

<table>
<thead>
<tr>
<th>Achalasia subtype</th>
<th>Type I Classic</th>
<th>Type II, with compression</th>
<th>Type III spastic</th>
<th>All types</th>
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<tr>
<td>First Intervention</td>
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<tr>
<td>Botulinum toxin</td>
<td>0% (0/2)</td>
<td>86% (67/7)</td>
<td>22% (2/9)</td>
<td>39% (7/18)</td>
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<tr>
<td>Pneumatic dilation</td>
<td>38% (3/8)</td>
<td>73% (19/26)</td>
<td>0% (0/11)</td>
<td>53% (24/45)</td>
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<tr>
<td>Heller Myotomy</td>
<td>67% (4/6)</td>
<td>100% (13/13)</td>
<td>0% (0/1)</td>
<td>85% (17/20)</td>
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<tr>
<td>All (any)</td>
<td>44% (7/16)</td>
<td>83% (38/46)</td>
<td>9% (2/21)</td>
<td>56% (47/83)</td>
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</table>

Subsequent interventions

| Number of interventions | 1.6±1.5 | 1.2±0.4* | 2.4±1.0* | 1.8±0.17 |
| Success last intervention | 56% | 96% | 29%*+ | 71% |
| Last intervention type | B-O, P-10, M-6 | B-6, P-25, M-15 | B-8, P-8, M-5 | B-14, P-43, M-26 |

*p<0.05 vs Type I, *+p<0.05 vs Type III

Pandolfini JE et al, Gastroenterology 2008;135:1526
Case 2

- 54-year-old male with mild hypertension and hypercholesterolemia
- Long-standing GERD symptoms are post-prandial heartburn and acid regurgitation
- Treated by primary care provider with H₂RAs and subsequently PPIs with nearly complete relief of heartburn but chest pain and regurgitation persist. Taking esomeprazole 40 qd at presentation
- ECG an exercise stress test reveal no evidence of CAD
- BMI 31 and patient has gained 15 pounds in the past two years by his account
- No prior surgery
- Endoscopy: Small hiatal hernia, no esophagitis
- Manometry: to be shown

Pressure Topography Plot

Conventional line tracings

Hypertensive Peristalsis
IRP = 9 mmHg
DCI = 6.131 mmHg-cm-s
CFV = 6 cm/s

Nutcracker Esophagus
Normal LES relaxation
Velocity 6 cm/s
Peak distal amplitude 250 mmHg
Case 2

- Calcium channel blockers
- Trial of twice daily esomeprazole for 2-4 wks
- Tricyclic antidepressants in low dose
- Ambulatory pH/impedance study taking esomeprazole
- Ambulatory pH/impedance study holding esomeprazole

After the patient did no better on 4 weeks of twice daily esomeprazole, an ambulatory pH/impedance study is done having him hold his esomeprazole treatment for 5 days prior. That was associated with some return of heartburn and a slight worsening of his chest pain. Regurgitation worsened as well, in the sense that it regained acidity that had not been pronounced while taking the esomeprazole.

The study showed 9% esophageal acid exposure (12 % during the day and 8% at night). The patient experienced 1 episode of chest pain during the study that did not occur within 2 minutes of a reflux event.
Case 2

- Further increase PPI therapy
- Refer to a cardiologist
- Tricyclic antidepressants in low dose
- Repeat the study on PPI therapy
- Refer for laparoscopic fundoplication
- Advise weight loss, continued bid (or qd) PPI

Case 3

- 45-year-old white female
- 3 year history of substernal burning, now daily. Some nocturnal symptoms
- No regurgitation or dysphagia
- Rare “globus sensation”
- Omeprazole 20 mg daily, esomeprazole 40mg daily, now dextansoprazole 60mg plus 150 mg ranitidine HS not satisfied
Case 3

- Barium swallow narrow esophagus
- Endoscopy normal mucosa
- Biopsy no eosinophils
- Ambulatory pH study followed by manometry

Options for Work Up

- What are likely findings on EGD?
- Ambulatory pH on or off therapy?
- Is impedance/pH required?
- Is manometry needed?
When are patients taking PPIs?

- 29.6% As needed
- 38.9% > 60 minutes before meals
- 27.8% After meals
- 3.7% At bedtime

Should pH (Reflux) Monitoring Be Performed Off or On Therapy?

- Low pre test probability of GERD at baseline/endoscopy not done
  - OFF Medication (7-10 days)
- GERD likely so need to assess efficacy of treatment/normal EGD
  - ON Medication (impedance/pH)

Role of Nonacid Reflux in NERD: Impedance/pH Monitoring in 150 Patients off Therapy

Ambulatory pH: 48 hours off therapy

- Time esophageal pH<4 normal day 1, 2 and overall
- DeMeester score normal day one/ 16 day two
- Total symptom episodes: heartburn 10, globus 3
- SI=20%, SAP=75% (both negative)
- Manometry normal
Options

• Add metoclopramide/sucralfate
• Add Baclofen
• Add Imipramine (or other tricyclic)
• Continue PPI indefinitely

Case 4

• 36-year-old with hoarseness, throat clearing, decreased voice strength
• Heartburn once or twice a month
• Opera singer, smokes a few cigarettes/day
• ENT exam: arytenoid erythema, edema, cobblestoning; no granuloma
Case 4

• Esomeprazole 40mg BID, minimal relief
• Dexlansoprazole 60mg BID plus H2 slight improvement
• Transnasal EGD ? Barrett’s

Next Steps

• Repeat sedated EGD (normal)
• 24 hour pH (and impedance?) on therapy?
• Prolonged telemetry capsule off therapy?
• Tell the patient it is not GERD and discharge after EGD
**pH Monitoring in Symptomatic Patients on Therapy May Be Abnormal**

- **Typical GERD (n = 175)**
- **Atypical GERD (n = 145)**


**MII-pH in Patients on PPI BID**

- **Symptoms**
  - 172 (86%)
  - No symptoms
    - 28 (14%)
    - Test Not Helpful

- **Possible GERD**
  - +SI Non-acid
    - 61 (35%)
  - +SI Acid Reflux
    - 13 (8%)

- **Likely GERD**
  - Symptoms with -SI
    - 98 (57%)
    - NOT GERD

MII/pH on Treatment Stratified By Symptoms

Typical GERD Symptoms (N=99)
- No reflux: 41%
- Non-acid: 48%
- Acid: 11%

Atypical GERD Symptoms (N=73)
- No reflux: 78%
- Non-acid: 19%
- Acid: 3%

p < 0.01

Non Acid Reflux and Positive Symptom Index

Patients with positive symptom index (%)
- Regurgitation: 72%
- Heartburn: 35%
- Cough: 32%
- Chest pain: 16%
- Abdominal Sx: 14%
- ENT symptoms: 10%
- Others: 22%

Symptom improvement and resolution after LARS among those presenting with the symptom

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Improved %</th>
<th>Resolution %</th>
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<tbody>
<tr>
<td>Heartburn</td>
<td>67</td>
<td>23</td>
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<tr>
<td>Regurgitation</td>
<td>70</td>
<td>22</td>
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<tr>
<td>Dysphagia</td>
<td>57</td>
<td>18</td>
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<tr>
<td>Cough</td>
<td>40</td>
<td>29</td>
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<tr>
<td>Hoarseness</td>
<td>47</td>
<td>22</td>
</tr>
</tbody>
</table>

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

- Intense mucosal eosinophilic infiltrate
- Eosinophilic microabscess

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!
### Topical steroids – eosinophil counts

**Graph:**
- **Pre-treatment** vs **Post-treatment**
- **X-axis:** Eosinophil count (eos/hpf)

<table>
<thead>
<tr>
<th>Year</th>
<th>Design</th>
<th>Subjects</th>
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<th>Rx time</th>
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<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>
<td>12 wks</td>
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<tr>
<td>2010</td>
<td>RCT</td>
<td>36 adults</td>
<td>Bud 2mg/d**</td>
<td>15 days</td>
</tr>
<tr>
<td>2010</td>
<td>RCT</td>
<td>24 children</td>
<td>Bud 1-2mg/d***</td>
<td>3 mos</td>
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<tr>
<td>2012</td>
<td>RCT</td>
<td>42 adults</td>
<td>FP 1760/d</td>
<td>6 wks</td>
</tr>
<tr>
<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

Pharmacologic therapy
- Corticosteroids *(systemic; topical)*
- Leukotriene antagonists (montelukast)
- Mast cell stabilizers (cromolyn)
- Immunosuppressants (6-MP; azathioprine)
- **Biologics** *(anti-IL-5; anti-IL-13; anti-IgE; anti-TNF)*
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Dietary therapy
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**EoE treatment options**

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**Dietary therapy**

**Endoscopic therapy (dilation)**

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**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 Jesus Gonzalez-Cervera,2 José M. Tenias,3 and Alfredo J. Lucendo4

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

Elemental diet - adults

Elemental Diet Induces Histologic Response in Adult Eosinophilic Esophagitis

- 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
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

Cow’s Milk Elimination: A Novel Dietary Approach to Treat Eosinophilic Esophagitis

• 65% response rate (≤ 15 eos/hpf)
• 64% response rate (< 15 eos/hpf)

Prospective, comparative effectiveness trial of cow’s milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis

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)
EoE treatment options

Pharmacologic therapy
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- Small molecules (CRTH2 antagonist)
- New directions

Dietary therapy
- Endoscopic therapy (dilation)

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>36</td>
<td>3 (8)</td>
<td>1 (3)</td>
<td>7 (19)</td>
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</table>

(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, 2008; Riou, Ann Thorac Surg, 1996)

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n*</th>
<th>Perfs</th>
<th>Boerhaave’s (spontaneous)</th>
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<td>17**</td>
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</table>

* 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:**

  ![Graph showing % without dysphagia over months](image)

- 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**

1. **New EoE diagnosis**
   - **Stricture present**
   - **Dilation**
   - **Non-response**
     - **Stricture present**

2. **Topical steroids or dietary elimination**
   - **Response**
   - **Non-response**
     - **Maintenance therapy**

3. **Assess compliance**
   - **Further diet restriction**
   - **Increase steroid dose or change formulation**
   - **Switch from steroids to diet or from diet to steroids**
   - **Consider second line agents or clinical trials**
   - **Exclude infection and reconsider other causes of esophageal eosinophilia**

*Dellon & Liacouras, Gastro, 2014*
WHAT A PAIN IN THE CHEST PAIN
Treatment of Esophageal (Noncardiac) Chest Pain

Michael F. Vaezi, MD, PhD, MSc(Epi)

Professor of Medicine and Otolaryngology
Clinical Director, Division of Gastroenterology
Director, Center for Swallowing and Esophageal Disorders
Director, Clinical Research
Vanderbilt University Medical Center

CHEST PAIN

Cardiac catheterization:
normal in 20% to 30%
over 200,000/yr

Non-Cardiac Chest Pain
Diminished quality of life
Overuse health-care resources
GERD in 10% to 50%
Non-cardiac Chest Pain
Definition

Recurring angina-like substernal chest pain of non-cardiac origin

Community-based Prevalence Rates of Noncardiac Chest Pain Around the World

Eslick G, in Fass and Eslick, NCCP—A Growing Medical Problem 200
Health Care Utilization

- See a physician for chest pain: 75%
- Unemployed: 50%
- Poor quality of life: 50%
- On cardiac meds: 50%
- Reassured: 30%


Noncardiac, Nonesophageal Chest Pain

Musculoskeletal
- Tietze’s syndrome
- Costochondritis
- Fibromyalgia
- Precordial catch syndrome
- Slipping rib syndrome

Gastrointestinal
- Gastric
- Biliary tree
- Pancreatic
- Intra-abdominal masses

Pulmonary
- Pneumonia
- Pulmonary embolus

- Lung cancer
- Pneumothorax and pneumomediastinum
- Pleural effusions
- Intrathoracic masses

Miscellaneous
- Aortic disorders
- Pericarditis and myocarditis
- Pulmonary hypertension
- Herpes zoster
- Drug-induced pain
- Sickle cell crisis
- Psychological disorders

Achem and DeVault, in Fass and Eslick, NCCP: A Growing Medical Problem 2007
Patients Admitted with Acute Chest Pain Not Myocardial Infarctions

All Diagnoses (%)

- Microvascular Angina (syndrome X)
- Musculoskeletal disorders
- Psychological disorders
- Pulmonary/Pericardial disorders
- Biliary/Gastric disorder
- Gastrointestinal diseases

Non Cardiac Chest Pain

- GERD
- Spastic Disorders
- Visceral Hyperalgesia

NON-CARDIAC CHEST PAIN
GERD MOST COMMON CAUSE

<table>
<thead>
<tr>
<th></th>
<th>Pain with Abnormal</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Motility</td>
<td>24-Hour pH</td>
</tr>
<tr>
<td>Janssen</td>
<td>60</td>
<td>13%</td>
<td>22%</td>
</tr>
<tr>
<td>Nevens</td>
<td>37</td>
<td>3%</td>
<td>14%</td>
</tr>
<tr>
<td>Hewson</td>
<td>45</td>
<td>22%</td>
<td>31%</td>
</tr>
<tr>
<td>Soffer</td>
<td>20</td>
<td>5%</td>
<td>45%</td>
</tr>
<tr>
<td>Hewson</td>
<td>100</td>
<td>ND</td>
<td>44%</td>
</tr>
<tr>
<td>Ghillebert</td>
<td>50</td>
<td>8%</td>
<td>30%</td>
</tr>
<tr>
<td>Paterson</td>
<td>25</td>
<td>28%</td>
<td>40%</td>
</tr>
<tr>
<td>DeCaestecker</td>
<td>50</td>
<td>ND</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>387</strong></td>
<td><strong>13%</strong></td>
<td><strong>50%</strong></td>
</tr>
</tbody>
</table>

NCCP and GERD Symptoms
Olmsted County Residents

Prevalence of GERD-Related Abnormalities in NCCP


GERD-RELATED CHEST PAIN
Clinical Features

Mimics angina
squeezing/burning
substernal
radiating to back, jaw, neck, or arms
worse after meals or supine position
lasts minutes to hours
intermittent
resolve with antacids
GERD-RELATED CHEST PAIN
Diagnostic Tests

- Barium study
- Endoscopy (Often Normal)
- Manometry
- Acid Perfusion (Bernstein) Test
  sensitivity: 36%
  specificity: 90%
- Ambulatory pH Monitoring
  sensitivity: 93%
  specificity: 71%
- PPI Test
### Prevalence of Endoscopic Findings in NCCP

**Large Multicenter Consortium**

<table>
<thead>
<tr>
<th>Findings</th>
<th>Chest Pain Group N = 3688 (%)</th>
<th>Reflux Group N = 32,981 (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett’ s</td>
<td>163 (4.4%)</td>
<td>3016 (9.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Esophageal inflammation</td>
<td>715 (19.4%)</td>
<td>9153 (27.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>1053 (28.6%)</td>
<td>14,775 (44.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normal</td>
<td>1627 (44.1%)</td>
<td>12,801 (38.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stricture/Stenosis</td>
<td>132 (3.6%)</td>
<td>1223 (3.7%)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

**NON-CARDIAC CHEST PAIN**

**ESOPHAGEAL MOTILITY**

- Normal Motility: 72%
- Nutcracker: 13%
- NEMD: 10%
- DES: 3%
- Hypertensive LES: 1%
- Achalasia: 1%

**GERD-RELATED CHEST PAIN**

*Placebo-Controlled Trial*

- Omeprazole: 81% Sx Improved (p = 0.001)
- Placebo: 6% Sx Improved

Achem et al. Gastroenterol. 1993; 104:51
OMEPRAZOLE TEST

- Sensitivity: 78%
- Specificity: 86%


PPI Therapy and Chest Pain Meta Analysis

- Symptom Improvement
- Symptom Resolution

Cremonini et al. AJG 2005; 100:1226-32.
PPI Therapy and Chest Pain
Meta Analysis

Presence of Abnormal Acid

> 50% Improvement

Cremonini et al. AJG 2005; 100:1226-32.

Chest pain and Nifedipine

N = 20 pts with nutcracker esophagus

- Distal Amplitude (mm Hg)
  - Placebo Nifedipine: *
  - Symptom Score
  - Placebo Nifedipine: NS

* p < .05

Richter et al Gastroenterology 1987; 93:21-8

Botulinum Toxin in DES

- 6-studies (1996-2009)
  - 5 observational
  - 1 sham-controlled
- Tx dose- 80-100 units
- Dysphagia improvement (6/6 trials)
- Long-term response: 50-100%
- No complications
Double Blind Randomized Controlled Study

Cross over trial
22 pts - spasm/nutcracker
Improved dysphagia

Vanuystel et al. CGH 2013; 11-1115-21

Improved Dysphagia Scores
No Change in Chest Pain

Vanuystel et al. CGH 2013; 11-1115-21
Proposed Mechanisms Functional Chest Pain

Abnormal mechanophysical properties
- Hyperactive
- ↓ Compliance

Sustained longitudinal muscle contractions

Visceral hypersensitivity
- Altered central and peripheral processing of visceral stimuli
- Altered autonomic activity

Psychological abnormalities
- Anxiety
- Depression

High-Frequency Intraluminal Ultrasonography
Esophageal Pain

Duration of esophageal contraction

Sustained Esophageal Contraction

Psychological Comorbidity

Psychological comorbidity, such as depression, panic disorder, and anxiety, is common in NCCP patients.

Treatment for Functional Chest Pain

- Tricyclic antidepressants
- Trazadone
- Selective serotonin reuptake inhibitors
- Adenosine antagonists
- Cognitive behavioral therapy
- Hypnotherapy
Chest pain and Trazodone

N = 29 pts with abnormal motility (DES, NE)

Clouse et al Gastroenterology 1987; 92:1027-36

Antidepressants and Chest Pain

Nguyen and Eslick. APT 2012; 35:493-500
Antidepressants and Chest Pain

<table>
<thead>
<tr>
<th>Pain reduction</th>
<th>Global health improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Venlafaxine</td>
<td>1. Venlafaxine</td>
</tr>
<tr>
<td>2. Sertraline</td>
<td>2. Sertraline</td>
</tr>
<tr>
<td>3. Imipramine</td>
<td>3. Trazodone</td>
</tr>
<tr>
<td>4. Trazodone</td>
<td>4. Imipramine</td>
</tr>
<tr>
<td>5. Paroxetine</td>
<td>5. Paroxetine</td>
</tr>
</tbody>
</table>

Nguyen and Eslick. APT 2012; 35:493-500

Citalopram 20mg Once Daily Vs. Placebo Hypersensitive Esophagus

A randomized, double-blind, placebo-controlled trial for 6 months.
% of patients who continued to report symptoms after full course of treatment

![Bar chart showing % of Patients](Viazis Am J Gastro 2012)
Hypnotherapy and Chest Pain

![Graph showing comparison between Supportive Therapy and Hypnotherapy for chest pain and general well-being.]

- % of Patients Reporting Improvement
  - Chest Pain: Supportive Therapy (p = 0.008), Hypnotherapy (p = 0.023)
  - General Well-being: Supportive Therapy, Hypnotherapy

Jones et al, Gut 2006;55:1403-1408

TREATMENT ALGORITHM

- CHEST PAIN
  - R/o Cardiac Disease
    - EGD (Alarm Sx’s)
      - Improved: TITRATE DOWN
      - Poor Response: MANOMETRY
        - Treat Motility Disorder
        - Pain Modulators
      - PPI TEST
Advanced Endoscopic Techniques in the Evaluation of Barrett’s Esophagus: Where Do They Fit?

Vani J.A. Konda, MD
Director of Endoscopic Research & Educational Programs
Center for Endoscopic Research & Therapeutics
University of Chicago Medicine

Goal:
To understand how we can perform optimal Barrett’s assessments to improve early identification of esophageal cancer or dysplasia

In our metaphoric puzzle, how do all the “pieces” fit together to provide a complete picture?
Esophageal Adenocarcinoma (EAC) is Rising

The key to decreasing esophageal cancer mortality is early detection and opportunity to intervene.

Barrett’s Esophagus (BE)

- Barrett’s esophagus is the replacement of normal squamous lining with specialized intestinal metaplasia.
- BE is a known risk factor for esophageal adenocarcinoma.
- BE is a complication of chronic reflux.
Endoscopic Screening

- Screening endoscopy to identify who has BE
- Not recommended for general population
- Select populations with multiple risk factors
  - Caucasian
  - Males
  - >50
  - Chronic Reflux / PPI
  - Hiatal hernia
  - Central obesity
  - Cigarette smoking
  - Family history

Barrett’s Esophagus Diagnosis

- Endoscopy
  - Salmon colored lining
  - In the tubular esophagus
  - Perform at least 8 biopsies
- Histologic criteria
  - Specialized intestinal metaplasia
  - Columnar lined epithelium with goblet cells
Irregular or Variable Z line

- Less than 1 cm
- Possible intestinal metaplasia of the cardia
- Not associated with same increased risk of esophageal cancer
- Avoid biopsy of the variable Z line

Surveillance

- Confirm no dysplasia
  - Biopsy protocol to evaluate for dysplasia
  - If insufficient biopsies on initial endoscopy, then may repeat within one year
- Monitor for dysplasia
  - Repeat EGD with biopsies every 3 – 5 years
### Spectrum of Pathology

<table>
<thead>
<tr>
<th>Squamous Epithelium</th>
<th>Barrett's Esophagus</th>
<th>Low Grade Dysplasia</th>
<th>High Grade Dysplasia</th>
<th>Intramucosal Cancer</th>
<th>Invasive Adenocarcinoma</th>
</tr>
</thead>
</table>

High inter-observer variability among pathologists in diagnosis of dysplasia

Confirm all cases with dysplasia with an expert gastrointestinal pathologist

### High Quality Endoscopic Assessment for BE “5 L’s”

- **Landmarks**: *Endoscopic Landmarks*
- **Length**: *Segment Length*
- **Lesions**: *Visible Lesions*
- **Look**: *Look Carefully for Subtle Lesions with High Resolution Endoscopy*
- **Levels**: *Random Biopsies at Multiple Levels*
1st L: Landmarks

Identify and Document

Diaphragmatic Impression
Gastroesophageal Junction
Squamocolumnar Junction

Normal
Hiatal Hernia
Barrett’s Esophagus

Landmarks are the corner pieces.
### 1st L: Landmarks

<table>
<thead>
<tr>
<th>Normal</th>
<th>Hiatal hernia</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Image 1]</td>
<td>[Image 2]</td>
</tr>
<tr>
<td>[Image 3]</td>
<td>[Image 4]</td>
</tr>
</tbody>
</table>

- **Diaphragmatic impression**
- **Gastroesophageal Junction**
- **Squamocolumnar Junction**

### 2nd L: Length

<table>
<thead>
<tr>
<th>Long Segments</th>
<th>Short Segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 cm or greater</td>
<td>1 cm or greater and less than 3 cm</td>
</tr>
</tbody>
</table>

- Long segments have a greater risk of progression to cancer compared to short segments.
2nd L: Length

Proper assessment of segment length provides the framework.


3rd L: Lesions

Identify and Target Visible Lesions

- Masses, nodules, ulcers, erosions, strictures, and flat lesions.
- Visible lesions have a risk for prevalent neoplasia and should be targeted for tissue acquisition.

Visible lesions are the biggest piece of the puzzle.
3rd L: Lesions

Document with Paris Classification


4th L: Look

You do not detect what you see, but what you recognize.

- Train the eye to recognize
- Use high resolution endoscopes
  - 800,000-1 million pixels
  - Superior to standard definition
- Examine mucosa en fosse
- Consider a soft transparent cap

A careful inspection with high resolution endoscopy can identify most high risk lesions.
Vani J.A. Konda, MD

REGULAR APPEARING BARRETT’S MUCOSA

SUSPICIOUS APPEARING BARRETT’S MUCOSA

4th L: Look
Train your eye and your exam
5th L: Levels

- Seattle Protocol
  - Visible lesions
  - Multiple levels for occult disease
    - random 4QB q1-2 cm
    - q1 cm if history of dysplasia
- Sampling error
- Poor adherence with protocol
  - Associated with increased risk of missed neoplasia.

Adhere to biopsy protocols to ensure no missing parts of your assessment.

Clinical Applications of Advanced Imaging

- Surveillance:
  - Can we improve detection of dysplasia & reduce number of negative biopsies?
- During Therapy:
  - Can we better guide treatment?
- Post Therapy Surveillance:
  - Can we detect residual or recurrent disease?
- Screening:
  - Can we improve esophageal cancer screening?
Clinical Applications of Advanced Imaging

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Digital Chromoendoscopy

- Narrow band imaging (NBI)
- Post processing systems: i-scan & FICE
- Mucosal & vascular pattern enhancement

Color enhancement with digital chromoendoscopy makes lesions easier to classify.
Vani J.A. Konda, MD

Digital Chromoendoscopy

- Multiple classification systems
- Improves diagnostic yield of dysplasia
- Meta analysis (NBI): detection of HGD per patient
  - 91% sensitivity
  - 95% specificity
- Accuracy improves when there is high confidence

Suspicious for neoplasia
- Irregular, distorted mucosal pattern
- Irregular vascular pattern

NBI with near focus
Endomicroscopy

- **Technologies**
  - Confocal Laser Endomicroscopy
  - Optical Coherence Tomography based technology
- **Provides real time tissue assessment at the micro architectural level.**
- **Potential for “smarter biopsies”**
  - Target neoplastic tissue
  - Reduce negative biopsies
  - Improve yield

*Endomicroscopy provides an “optical biopsy” to detect subtle lesions.*

### Endomicroscopy Technology System Depth Resolution Span

<table>
<thead>
<tr>
<th>Technology</th>
<th>System</th>
<th>Depth</th>
<th>Resolution</th>
<th>Span</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscope based CLE (eCLE) (not available)</td>
<td>Confocal Laser Endomicroscopy (CLE)</td>
<td>0 – 250 microns</td>
<td>0.7 micron</td>
<td>550 microns</td>
</tr>
<tr>
<td>Probe Based CLE (pCLE) (commercially available)</td>
<td>Confocal Laser Endomicroscopy (CLE)</td>
<td>65 microns</td>
<td>1 micron</td>
<td>240 microns</td>
</tr>
</tbody>
</table>

ACG 2015 Annual Postgraduate Course
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# Endomicroscopy

<table>
<thead>
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## Confocal Laser Endomicroscopy

- Criteria development, validation & refinement
  - Miami Classification, Kansas Criteria
- CLE Meta-analyses, Per Patient, detection of dysplasia
  - 86-89% Sensitivity and 75-83% Specificity

Multimodal Imaging for Subtle Lesions

- Multimodal imaging HRE/NBI/CLE:
  - Red flag \( \text{NBI} \)
  - Close inspection \( \text{CLE} \)
- Multicenter trial HRE/NBI/CLE:
  - 100% sensitivity & 100% NPV

Endomicroscopy

<table>
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<tbody>
<tr>
<td>Endoscope based CLE (eCLE)</td>
<td>Confocal Laser Endomicroscopy (CLE)</td>
<td>Scope &amp; processor</td>
<td>0 – 250 microns</td>
<td>0.7 micron</td>
</tr>
<tr>
<td>Probe Based CLE (pCLE)</td>
<td>Confocal Laser Endomicroscopy (CLE)</td>
<td>Probe</td>
<td>65 microns</td>
<td>1 micron</td>
</tr>
<tr>
<td>Volumetric Laser Endomicroscopy</td>
<td>Optical coherence tomography (OCT)</td>
<td>Laser probe in balloon catheter</td>
<td>3mm</td>
<td>7 microns</td>
</tr>
<tr>
<td>(VLE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Endomicroscopy

<table>
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<td>Confocal Laser Endomicroscopy</td>
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<td>1 micron</td>
<td>240 microns Video</td>
</tr>
<tr>
<td></td>
<td>(CLE) Probe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volumetric Laser Endomicroscopy</td>
<td>Optical coherence tomography (OCT)</td>
<td>3mm</td>
<td>7 microns</td>
<td>6 cm span cross-sectional</td>
</tr>
<tr>
<td>(VLE)</td>
<td>Laser probe in balloon catheter</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VLE

- Safe, feasible
- Detection of Squamous vs. Barrett’s with excellent IOV
- Criteria under development and validation
- Histological correlation feasible

Wolfsen et al. GIE 2015; Sauk et al DDS 2013; Leggett et al. GIE 2015; Swager et al. Dis Eso 2015
VLE detection of HGD

- Loss of layering
- Septated glands
- Irregular surface

Other Advanced Imaging

- Chromoendoscopy
- Auto fluorescence Imaging (AFI)
  - Not available in US
# Risk Stratification

## Risk

<table>
<thead>
<tr>
<th>Risk</th>
<th>Barrett's No Dysplasia</th>
<th>Barrett's Low Grade Dysplasia</th>
<th>Barrett's High Grade Dysplasia</th>
<th>Intra-mucosal Cancer</th>
<th>Sub-mucosal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Incidence of Cancer</td>
<td>0.2 – 0.3%</td>
<td>0.5-0.7%</td>
<td>6-12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalent Occult Cancer</td>
<td>40%</td>
<td></td>
<td></td>
<td>Especially in Visible lesions</td>
<td></td>
</tr>
<tr>
<td>Lymph Node Metastasis</td>
<td>0%</td>
<td>1 - 2%</td>
<td>&gt;20%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Stratification provides the background to guide management.
Management

Non Dysplastic
- Short Segment
  - Surveillance 3 – 5 years
- Long Segment

Low Grade Dysplasia
- Low risk
  - Close Surveillance
- High risk

HGD / IMC
- + Submucosal invasion

Treatment
- Visible lesion
  - EMR
- Remainder / Flat
  - Ablation
- Surgery / Systemic therapy

Counseling

HGD

LGD

NDBE
Clinical Applications of Advanced Imaging

• **Surveillance:**
  – Can we improve detection of dysplasia & reduce number of negative biopsies?

• **During Therapy:**
  – Can we better guide treatment?

• Post Therapy Surveillance:
  – Can we detect residual or recurrent disease?

• **Screening:**
  – Can we improve esophageal cancer screening?

Endoscopic mucosal resection (EMR)

• Required for visible lesions, in setting of dysplasia, to rule out cancer.

• More accurate than biopsies or EUS
  – EMR changes the diagnosis in up to ½ of cases
  – EUS appropriate for N staging, but inadequate for early T staging.

• Advanced imaging may be used to target and define extent of resection.
Endoscopic mucosal resection (EMR)

- Required for visible lesions, in setting of dysplasia, to rule out cancer.
- More accurate than biopsies or EUS
  - EMR changes the diagnosis in up to ½ of cases
  - EUS appropriate for N staging, but inadequate for early T staging.
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- Surveillance:
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- During Therapy:
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- Post Therapy Surveillance:
  - Can we detect residual or recurrent disease?
- Screening:
  - Can we improve esophageal cancer screening?
Post-Treatment Surveillance

- Neither multicenter trials with NBI nor with CLE demonstrated prediction of residual disease after therapy.

- Reports of OCT based technologies have demonstrated detection of buried glands in naïve and post-treatment settings.

OCT potentially may allow detection of buried disease.

Clinical Applications of Advanced Imaging

- Surveillance:
  - *Can we improve detection of dysplasia & reduce number of negative biopsies?*

- During Therapy:
  - *Can we better guide treatment?*

- Post Therapy Surveillance:
  - *Can we detect residual or recurrent disease?*

- **Screening:**
  - *Can we improve esophageal cancer screening?*
Need Better Screening Tools

A non endoscopic screening method may identify all those patients we are missing.
Take Home Points (1/2)

- High Quality Barrett’s surveillance with 5L’s
  - Identify and Document Landmarks
  - Measure and Document Segment Length
  - Identify and Target Visible Lesions
  - Look carefully with high resolution endoscopy
  - Adhere to a biopsy protocol with multiple Levels

Take Home Points (2/2)

- In cases with Dysplasia:
  - Confirm dysplasia with an expert pathologist.
  - Visible lesions need endoscopic resection.

- Advanced imaging provides an increased, but incremental yield.

- Risk stratification and counseling are essential.

- Despite these advances, we are not capturing most with esophageal adenocarcinoma.
Thank you.