Treatment of Refractory GERD and Functional Chest Pain

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Step 1

PPI once daily for 2 months

Incomplete or lack of response

Review proper PPI dosing time and Compliance
Evaluate Lifestyle Modifications

GERD – A Symptom Driven Disease

I have heartburn

I will take my medication

Sub-Optimal Proton Pump Inhibitor Dosing is Prevalent in Patients with Poorly Controlled Gastro-Oesophageal Reflux Disease

27.8
3.7
29.6
38.9

>60 minutes before meals
After meals
At bedtime
As needed

N = 100

Gunaratnam et al. Aliment Pharmacol Ther 2006;23(10):1473-1477
### Lifestyle Modifications

<table>
<thead>
<tr>
<th>Factor</th>
<th>Trials, No.</th>
<th>Lowered LESP</th>
<th>Worsened pH</th>
<th>Worsened Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>12</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Alcohol</td>
<td>16</td>
<td>No effect (B)</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Obesity</td>
<td>24</td>
<td>E</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>Coffee and caffeine</td>
<td>14</td>
<td>E</td>
<td>E</td>
<td>No effect (C)</td>
</tr>
<tr>
<td>Chocolate</td>
<td>2</td>
<td>B</td>
<td>B</td>
<td>E</td>
</tr>
<tr>
<td>Spicy foods</td>
<td>2</td>
<td>E</td>
<td>E</td>
<td>C</td>
</tr>
<tr>
<td>Citrus</td>
<td>3</td>
<td>No effect (B)</td>
<td>E</td>
<td>C</td>
</tr>
<tr>
<td>Carbonated beverages</td>
<td>2</td>
<td>B</td>
<td>E</td>
<td>C</td>
</tr>
<tr>
<td>Fatty foods</td>
<td>9</td>
<td>D</td>
<td>B</td>
<td>E</td>
</tr>
<tr>
<td>Mint</td>
<td>1</td>
<td>D</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>Recumbent position</td>
<td>3</td>
<td>B</td>
<td>E</td>
<td>B</td>
</tr>
<tr>
<td>RLD position</td>
<td>3</td>
<td>B</td>
<td>B</td>
<td>E</td>
</tr>
<tr>
<td>Late evening meal</td>
<td>3</td>
<td>B</td>
<td>No effect</td>
<td>E</td>
</tr>
</tbody>
</table>


### Important Lifestyle Modifications
Step 2

Switch to another PPI/split the PPI dose (am+pm)

OR

Add another anti reflux modality to PPI

Double the PPI dose


Switching to Another PPI – Highly Successful

<table>
<thead>
<tr>
<th></th>
<th>Esomeprazole 40 mg once daily (N=138)</th>
<th>Lansoprazole 30 mg twice daily (N=144)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartburn symptom improvement, % (N) after 8 weeks</td>
<td>83.3 (155)</td>
<td>83.3 (120)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Percentage of Patients Symptomatically Controlled on twice daily PPI Who were Successfully Stepped-Down to Dexlansoprazole Once Daily

- In 88% (95% CI, 82.7%-93.4%; n=125) of the patients their heartburn remained well controlled after stepping down to once daily Dexlansoprazole 30mg MR.


Percentage of Patients who Remained Well Controlled after Stepping Down to Dexlansoprazole MR 30 mg by Prior PPI

<table>
<thead>
<tr>
<th>Prior PPI</th>
<th>% of patients who remaining well controlled, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>84.0 (21/25)</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>85.7 (12/14)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>88.1 (74/84)</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>100.0 (14/14)</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>87.5 (7/8)</td>
</tr>
</tbody>
</table>

Role of Prokinetic Agents in Refractory GERD

- Improve esophageal clearance and increase lower esophageal sphincter basal pressure.
- Provide an extra “kick” to a normally functioning stomach.

Proportion of Patients That Failed PPI Once Daily (Lansoprazole 30mg) Who Reported Complete Symptom Relief on PPI Twice Daily

Endoscopically Confirmed Healing Rates of Refractory Reflux Esophagitis after 8 weeks of Treatment


Step 3

Upper Endoscopy (?)

Wireless pH capsule/pH test off treatment

OR

Intraesophageal impedance + pH on treatment

American College of Physicians (ACP) Best Practice Advice

• Best Practice Advice 2

*Upper endoscopy is indicated in men and women with: Typical GERD symptoms that persist despite a therapeutic trial of 4 to 8 weeks of twice-daily PPI therapy*


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What Is the Value of an Upper Endoscopy in Patients Who Failed PPI Once Daily?

<table>
<thead>
<tr>
<th>Endoscopic findings</th>
<th>PPI failure (%) (N=105)</th>
<th>No treatment (%) (N=91)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>58 (55.2)</td>
<td>37 (40.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Erosive esophagitis</td>
<td>7 (6.7)</td>
<td>28 (30.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Barrett's esophagus</td>
<td>4 (3.8)</td>
<td>3 (3.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>1 (0.9)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Hiatal hernia</td>
<td>14 (13.3)</td>
<td>13 (14.3)</td>
<td>0.85</td>
</tr>
<tr>
<td>Esophageal ring</td>
<td>11 (10.5)</td>
<td>10 (11)</td>
<td>0.91</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>1 (0.95)</td>
<td>1(1.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Esophageal webs</td>
<td>1 (0.95)</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Poh CH et al. Gastrointest Endosc 2010;71:28-34
What can be Expected from Ambulatory pH Monitoring for Reflux “Off” Therapy?

- Document baseline abnormal esophageal acid exposure
- Classify the patient as having NERD or functional heartburn
- 48 – 96 hour recording with wireless pH capsule have increased diagnostic yield as compared to 24h pH test.

Impedance + pH test has very little value


What Can be Expected from Ambulatory Monitoring for Reflux on Therapy (PPI twice daily)

- Very low diagnostic yield of pH test alone as compared to impedance + pH
- Establish a correlation between symptoms and reflux events (SI and/or SAP)
- Exclude GERD as the cause of refractory heartburn (neg. SI and SAP)

“When you come to a fork in the road, take it.”

Yogi Berra

The Important Role of Impedance + pH in Patients’ Stratification

Symptomatic patients on PPI BID
172 (86%)

Nonacid reflux
61 (35%)

Acid reflux
13 (8%)

Symptoms not associated with reflux
98 (57%)

Step 4

Weakly acidic/alkaline reflux

↓

TLESR Reducer

Prokinetics

Pain modulators

Endoscopic treatment

Anti-reflux surgery

Linx


Baclofen – For Non-Acidic Reflux

- GABA-B agonists
- Reduces TLESR
- Mild gastrokinetic
- 40-50% reduction in TLESR rate
- Improve GERD symptoms
- Start with 10mg at bed time
- Can increase up to 20mg tid
- Watch for neurological side effects


The Stretta Technique

PPI’s and Antacids Use 48 Months after Stretta Procedure

Esophyx and Similar Techniques

Transoral Incisionless Fundoplication 2.0
Procedure Using Esophyx™ for Gastroesophageal Reflux Disease

- N = 19
- Patients - Typical GERD SX, failed PPI, abnormal pH test, positive SI, no Hiatal hernia > 2cm
- Outcome - 3/19 (16%) – major complications
  - After follow-up 10.8 months,
  - 10/19 (53%) – converted to lap fundoplication
  - 9/17 (53%) – dissatisfied with outcome
  - 13/19 (68%) – considered unsuccessful

Conclusions: Excessive early symptoms failure and a high surgical re-intervention rate.

Hoppo T et al. J Gastrointest Surg. 2010 Dec;14(12):1895-901
Antireflux Surgery in NERD and Erosive Esophagitis Patients Refractory to Treatment

<table>
<thead>
<tr>
<th></th>
<th>NERD</th>
<th>ERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>15.0 (1.7) (N=60)</td>
<td>12.7 (1.5) (N=81)</td>
</tr>
<tr>
<td>3 months</td>
<td>3.1 (0.7) (N=60)</td>
<td>2.1 (0.6) (N=81)</td>
</tr>
<tr>
<td>5 years</td>
<td>2.6 (1.0) (N=23)</td>
<td>0.9 (0.3) (N=21)</td>
</tr>
<tr>
<td>Positive SI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>47 of 57 (82%)</td>
<td>62 of 81 (77%)</td>
</tr>
<tr>
<td>3 months</td>
<td>2 of 57 (4%)</td>
<td>3 of 81 (4%)</td>
</tr>
<tr>
<td>5 years</td>
<td>3 of 24 (13%)</td>
<td>3 of 22 (14%)</td>
</tr>
<tr>
<td>Positive SAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>42 of 51 (82%)</td>
<td>63 of 79 (80%)</td>
</tr>
</tbody>
</table>


LINX™ Reflux Management System

Reinforces the LES restoring the barrier function

Expands during swallow allowing food to enter stomach

Highest Magnetic Resistance

Lowest Magnetic Resistance
**LINX – 3-Year Follow Up**

- Total participants 100
- Normalization or at least 50% reduction in acid exposure – 64%
- At least 50% reduction in PPI use – 93%
- At least 50% improvement in quality of life – 92%
- Limitations – not controlled, selective, only 50% with normal pH and dysphagia
- Unclear long-term consequences of a foreign body around the esophagus


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**Step 3**

**Residual acidic reflux**

- Review proper PPI dosing time and Compliance
- Evaluate Lifestyle Modifications
- Consider H2RA at bedtime

Always Remember other Putative Mechanisms in Refractory GERD

- Psychological co-morbidity
- Functional bowel disorders
- Delayed Gastric Emptying
- Eosinophilic esophagitis
- Skin disease with esophagitis
- Pill esophagitis


Functional Heartburn

Functional Chest Pain
Pain Modulation in PPI Failure - TCA Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>NE</th>
<th>5-HT</th>
<th>H₁</th>
<th>ACh</th>
<th>Initial</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>+2</td>
<td>+2</td>
<td>+4</td>
<td>+4</td>
<td>10-50</td>
<td>25-150</td>
</tr>
<tr>
<td>Imipramine</td>
<td>+2</td>
<td>+2</td>
<td>+4</td>
<td>+2</td>
<td>10-50</td>
<td>25-150</td>
</tr>
<tr>
<td>Desipramine</td>
<td>+4</td>
<td>+2</td>
<td>+1</td>
<td>+1</td>
<td>10-50</td>
<td>25-150</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>+3</td>
<td>+2</td>
<td>+2</td>
<td>+2</td>
<td>10-50</td>
<td>25-150</td>
</tr>
</tbody>
</table>

NE, norepinephrine; 5-HT, 5-hydroxytryptamine; H₁, histamine-H₁ receptor, Ach, acetylcholine.

Sperber AD, Drossman DA. *Aliment Pharmacol Ther* 2011;33:514-524

Tricyclic Antidepressants
Receptor Affinity Predicts Side Effects

Receptor Affinities*:

- **3° amines**
  - Amitriptyline
  - Imipramine
  - Doxepin

* For acetylcholine, histamine, and α-adrenergic receptors
Tricyclic Antidepressants
Receptor Affinity Predicts Side Effects

Receptor Affinities*

3° amines
- Amitriptyline
- Imipramine
- Doxepin

2° amines
- Nortriptyline
- Desipramine

* For acetylcholine, histamine, and α-adrenergic receptors

Tricyclics for Esophageal Pain

Tricyclics
- Amitriptyline (Elavil)
- Imipramine (Tofranil)
- Doxepin (Sinequan)
- Nortriptyline (Pamelor)
- Desipramine (Norpramin)
- Trimipramine (Surmontil)
- Clomipramine (Anafranil)
Tricyclics for Esophageal Pain

- Amitriptyline (Elavil)
- Imipramine (Tofranil)
- Doxepin (Sinequan)
- Nortriptyline (Pamelor)
- Desipramine (Norpramin)
- Trimipramine (Surmontil)
- Clomipramine (Anafranil)

SSRI’s for Esophageal Pain

- Fluoxetine (Prozac)
- Paroxetine (Paxil)
- Sertraline (Zoloft)
- Fluvoxamine (Luvox)
- Citalopram (Celexa)
- Citalopram isomer (Lexapro)
Other Antidepressants for for Esophageal Pain

- Venlafaxine (Efexor)
- Mirtazapine (Remeron)
- Bupropion (Wellbutrin)
- Trazodone (Desyrel)
- Nefazodone (Serzone)
- Reboxetine (Edronax)
- Duloxetine (Cymbalta)

Antidepressant Therapy for FGIDs

Side Effect Observations

- Many “side effects” are present pre-treatment
  
  *Dalton C, et al. Gastroenterology 2004(A)*

- Higher degrees of somatization predict antidepressant intolerance
  

- Drop-out rates in FGIDs exceed those seen in depression
  
  *Gill D & Hatcher S. Cochrane Database Syte Rev 2004*

- Central neurophysiological processes accompanying FGIDs may define propensity for side effects
Premature Antidepressant Discontinuation in FGIDs

Sayuk GS, et al. DDW 2006
Premature Antidepressant Discontinuation in FGIDs

Sayuk GS, et al. DDW 2006

How to Use TCAs in Practice

Main Principle: “Low and slow”

- Start 10 mg–25 mg at bedtime
- Increase by 10 mg–25 mg increments weekly
- Goal of treatment 50 mg–75 mg once daily
- If side effects emerge:
  - Decrease to a lower dose
  - Can switch to another TCA
- May combine with SSRIs
TCA’s - How Low Can You go?

- The new approach:
  - Dosing: 5 – 10mg at bed time for 3-4 weeks before increasing the dose.
  - Explain to patients that response may take time

The Effect of Citalopram 20mg Once Daily Vs. Placebo on Patients with the Hypersensitive Esophagus

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

*P=0.02

Viazis Am J Gastro 2012
Efficacy of Venlafaxine (75 mg qhs) vs. Placebo on the Mean Intensity Symptom Score in Functional Chest Pain


Hierarchy of Antidepressants for Esophageal Pain Reduction and Global Health Improvement

<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>

Other Pain Modulators

- Pregabalin
- Neurontin

Psychological Interventions for Functional Chest Pain

- 15 RCT’s (803 pts)
- Reports of chest pain first 3 ms RR=0.68 (95% CI 0.57 to 0.81) Maintained for 3 – 9ms RR = 0.59 (95% CI 0.45 – 0.76)
- Cognitive behavioral therapy (CBT) and hypnotherapy

Acupuncture

- ↓ GERD-related symptoms
- ↓ in intra-esophageal acidic reflux
- ↓ in intra-esophageal bile reflux
- ↓ endoscopic grading