The PPI Non-responsive patient

The Unresponsive and Refractory Patient: What to Do and How to Manage
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Northwestern Medicine
Northwestern Memorial Hospital

GERD is a condition which develops when the reflux of stomach content causes troublesome symptoms and/or complications

Symptomatic Syndromes
- Typical reflux syndrome
- Reflux chest pain syndrome

Syndromes with Esophageal Injury
- Reflux esophagitis
- Reflux stricture
- Barrett’s esophagus
- Adenocarcinoma

 Established Association
- Reflux cough
- Reflux laryngitis
- Reflux asthma
- Reflux dental erosions

Proposed Association
- Sinusitis
- Pulmonary fibrosis
- Pharyngitis
- Recurrent otitis media

Vakil N et al. Am J Gastroenterol 2006;101:1900
Determinants of Reflux Severity

**Primary pathophysiology**

- # of reflux events
- Acid clearance
- Causticity of gastric juice
- Tissue sensitivity

Esophagitis Severity ≈ reflux events X Acid clearance X Causticity of gastric juice X Tissue sensitivity

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**Determinants of Reflux Severity**

- **Not a primary abnormality of GERD**
- Symptom Triggers
- Symptom modulators
- Reflux events
- Acid clearance
- Acidity of gastric juice
- Tissue sensitivity

Symptom Triggers ≈ Reflux events X Acidity of gastric juice X Tissue sensitivity

Symptom modulators ≈ Reflux events X Acidity of gastric juice X Tissue sensitivity
Determinants of Reflux Severity

PPI therapy of GERD is compensatory, not curative

Targets of PPI therapy

- Symptom Triggers
- Acid clearance
- Reflux events
- Acidity of gastric juice
- Symptom modulators
- Tissue sensitivity

Intragastric pH Control on Once-Daily PPI

Mean hours intragastric pH > 4 on day 5

A correlation between pH data and clinical outcome has not been directly established

Mean hours intragastric pH > 4 on day 5

- Esomeprazole† 40 mg
- Omeprazole† 20 mg
- Lansoprazole 30 mg
- Pantoprazole 40 mg
- Rabeprazole 20 mg

*P < .0004 (N = 34, all pairwise comparisons vs esomeprazole)

Treating Reflux Disorders: An Updated Algorithm

Patient self-care fails, symptoms indicate GERD,
Endoscopy for warning signs / alternative diagnosis

Optimize TX
PPI therapy 4-8 weeks

Compliance

Success

Continue TX at current dose

Step down and stop; restart on lowest effective dose if relapse occurs

Success

Aim for lowest dose "on-demand therapy"

Success

Improve Acid suppression
"not FDA Approved"

Switch PPI

Double dose (Not approved)

Double dose PPI + H2 blocker

Refer to specialist

Always consider alternative diagnosis when treatment failure occurs


50% of GERD patients do not achieve symptom resolution on PPI

Kahrilas PJ...Response of regurgitation to PPI therapy in clinical trials of GERD. AJG, 2011;106(8):1419-25; PMID: 21537361.

Complete resolution at 4 weeks (95% CI)

'Oversternal burning' (entry criterion)

'Oversternal pain'

'Regurgitation-taste'

'Regurgitation movement'

NERD (n=1415)  RE (n=1460)

High severity symptoms (≥4 days/wk of at least moderate intensity)
PPI Failures

- Patients are typically sent for endoscopy
- Most patients with GERD will be EGD negative

The real GERD management issue in 2015 is:
- Refractory symptoms
  - 30-50% of patients are unsatisfied with symptom control.

Pathophysiology is heterogeneous and poorly understood

- PPI NR with pathological gastroesophageal reflux
  - Esophagitis
  - Barrett’s Esophagus [Well-defined based on mucosal injury-10-20%]
  - NERD [Heterogeneous: [compliance, PPI hypermetabolizer, severe anatomy, functional overlap-10-20%]]

- PPI NR without evidence of pathological gastroesophageal reflux
  - Functional heartburn
  - Reflux hypersensitivity (non-acid reflux)
  - Rumination/belching syndrome [Poorly defined: Functional Makes up largest proportion and presents the biggest problem]
New techniques have been limited in their ability to define mechanistic phenotypes

- **Combined catheter based pH-impedance**
  - Great value as a research tool.
  - No outcome measure that predicts likelihood to respond to surgery or escalation of therapy.
  - Phenotype description is flawed by its reliance on symptom-reflux correlation.
  - Major insurers are not covering this device.

- **Bravo- prolonged wireless pH monitoring**
  - Prolonged studies may be able to rule out GERD.
  - Value is focused mainly on documenting acid exposure off medications and potentially stopping PPI.

- **Mucosal impedance probe**
  - New methodology that can be performed in less than 5 minutes during endoscopy.
  - Not validated against the “gold standard”

Management approach is too complicated and not cost-effective
Management approach is too complicated and not cost-effective


• **Cost**
  – Endoscopy- ($3,000)- repeated unnecessarily.
  – Reflux testing ($500-1000)- may need to be repeated if not used appropriately.
  – Multiple Clinic visits for testing and empiric trials.

• **Patients continue to use PPI despite no evidence of pathologic acid exposure**
  – Half of the patients not responding to PPI have no evidence of abnormal acid exposure or a reflux correlation with symptoms.
  – Dose escalation does not work in the majority of patients.
**PPI NR Work up - Simple Approach**

Patients failing optimized compliant PPI therapy

- EGD performed to assess anatomy and stratify GERD severity * no alternative diagnosis
- Reflux testing off PPI with Bravo or pH-impedance. Consider HRIM if belching/rumination/motor disorder considered

**Esophagitis**

- Yes-60%
- No-60%

**GERD**

- Abnormal
- Normal

**Optimize PPI**

- Behavioral/Meditative Reflux inhibitors

**No response**

- Further work-up [pH-impedance/HRIM]

**Phenotyping PPI Non-responders:**

Low pre-test probability of refractory GERD

**Wireless pH testing**

**Phenotyping PPI Non-responders:**

High pre-test probability of refractory GERD pH-impedance monitoring

---

**PPI NR Work up- Simple Approach**

Patients failing optimized compliant PPI therapy

EGD performed to assess anatomy and stratify GERD severity + rule out alternative diagnosis

Reflex testing off PPI with Bravo or pH-impedance: Consider HRM if belching/rumination/motor disorder correlated

Abnormal Reflux Sensitivity

Functional Heartburn

Alternative DX

No response: Further workup (HRM, Alternative DX)

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Focus of therapy on Functional Heartburn and Reflux Sensitivity should be on the appropriate targets

- Regardless of phenotype, the management approach of patients with a failure to respond to PPIs should be focus on techniques aimed at reducing visceral sensitivity and hypervigilance.

<table>
<thead>
<tr>
<th>Hypnotherapy</th>
<th>Neuromodulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>High upfront</td>
</tr>
<tr>
<td>Risks</td>
<td>Negligible</td>
</tr>
<tr>
<td>Acceptability</td>
<td>Good</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Poor</td>
</tr>
<tr>
<td>Availability</td>
<td>Limited</td>
</tr>
<tr>
<td>Target</td>
<td>Cognitive-affective processes, hypersensitivity hypervigilance and pain</td>
</tr>
<tr>
<td></td>
<td>Pain only</td>
</tr>
</tbody>
</table>

**PPI NR Work up- Simple Approach**

1. Patients failing optimized compliant PPI therapy
2. EGD performed to assess anatomy and stratify GERD severity
3. R/o alternative diagnosis
4. pH-Impedance/HRIM if belching/rumination/motor disorder entered

**Esophagitis**

- Yes-40%
  - GERD
  - Optimize PPI
  - Behavioral/Lifestyle
  - Reflux Inhibitors?
  - No response
    - Further work-up (pH-Impedance/HRIM)
Reflux-symptom Association on PPI Therapy

Mechanism of PPI failure

168 patients with symptoms

Symptoms 144 (85%)
No symptoms 24 (15%)

Positive SI 69 (48%)

Negative SI 75 (52%)

Functional Alternative DX

Acid Breakthrough

+SI acid 16 (11%)
+SI non-acid 53 (37%)
Non-Acid Reflux


Determinants of Refractory Reflux

PPI Failures

Abnormal in number, composition, or volume refluxed

Symptom Triggers
Symptom modulators

Reflux events
Acid clearance

Acidity of gastric juice

Tissue sensitivity

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Antireflux Surgery in GERD

**Indications**

*When antireflux surgery and PPI therapy are judged to offer similar efficacy in a patient with an esophageal GERD syndrome, PPI therapy should be recommended as initial therapy because of superior safety.*

I. When a patient with an esophageal GERD syndrome is responsive to, but intolerant of, acid suppressive therapy, antireflux surgery should be recommended as an alternative.

II. Antireflux surgery for patients with an esophageal GERD syndrome with persistent troublesome symptoms, especially troublesome regurgitation, despite PPI therapy.
   1. Must have proven GERD.
   2. The potential benefits of antireflux surgery should be weighed against the deleterious effect of new symptoms consequent from surgery, [dysphagia, gas bloat, IBS].

Endoscopic Therapies for GERD

**Guidelines/Position Statements**

**AGA GERD Guidelines 2008:**
The use of currently commercially available endoluminal antireflux procedures in the management of patients with an esophageal syndrome.
*(Insufficient evidence to recommend)*

**ACG Guidelines 2013:**
The usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy.
*(Strong recommendation, moderate level of evidence)*
Model for Symptom Generation in PPI Non-responders

Conceptual Model of PPI-NRs- 2012-2014

Defining Phenotypes of PPI Non-responder

Preliminary Data 2014-2015

| Hypervigilance is elevated but does not differ based on # reflux days positive |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                  | 0 Days (N = 37) | 1 day (N = 15)  | 2+ day (N = 18) | Test Statistic   |
| Symptom Index                    | 6.69 (11.3)b    | 64.6 (22.7)b    | 83.3 (17.5)b,c  | F(3, 66) = 165.1, p = .00 |
| Acid exposure time               | 6.4 (6.6)a      | 7.8 (6.1)       | 12.0 (4.6)b     | F(3, 66) = 5.1, p = .01 |
| GERDQ                            | 8.1 (2.3)       | 9.5 (3.5)       | 10.4 (2.7)      | F(3, 66) = 4.7, p = .01 |
| Catastrophizing                  | 23.7 (14.7)     | 27.0 (10.1)     | 29.9 (9.8)      | ns               |
| Hypervigilance                   | 50.0 (21.9)     | 60.9 (17.5)     | 53.7 (23.2)     | ns               |
| Visceral Anxiety                 | 48.6 (21.4)     | 42.9 (19.9)     | 46.5 (14.2)     | ns               |

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Model for Symptom Generation in PPI Non-responders

**New Conceptual Model of PPI-NRs**

Hypervigilance and Visceral Sensitivity are driving symptoms across all PPINRs

- **Refractory GERD**
  - Abnormal Acid exposure

- **Reflux Sensitivity**
  - Non-acid reflux

- **Reflux Sensitivity**
  - Normal reflux burden

- **Functional Heartburn**

**Continue PPI**
- Treatment targets escalating antireflux therapy
- [Higher PPI dose] and reducing reflux (weight loss)
- Neuromodulators and Behavioral techniques may also be helpful
- Surgery may be indicated as a last resort

**Continue PPI**
- Treatment targets encouraging weight loss and potentially
  - Neuromodulators and Behavioral techniques
  - 
  - reflux inhibition is secondary

**Discontinue PPI**
- Treatment targets Neuromodulators and Behavioral techniques

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**Northwestern Refractory GERD Approach**

Heartburn, Regurgitation, Chest Pain

**Document Compliance**

**EGD and possible reflux testing if EGD (-) and symptoms continue**

Consider motility (HRIM) testing for atypical presentation
- Rule out eating disorder/rumination

**Define Phenotype-Reflux Testing**

- **Proven Refractory Reflux**
  - Hernia
  - Optimize medications
  - Lifestyle modifications
  - Behavioral Intervention
  - Consider Intervention*
    - Hernia repair
    - Fundoplication

- **Proven Refractory Reflux**
  - Normal Motility
  - Optimize medications
  - Lifestyle modifications
  - Behavioral Intervention

- **Proven Reflux**
  - Functional HB/sensitivity
  - Optimize medications
  - Lifestyle modifications
  - Behavioral Intervention

- **Not Reflux**
  - Functional HB/ sensitivity*
  - Stop PPI
  - Lifestyle modifications
  - Behavioral Intervention
  - Neuromodulator

- **Baclofen/Neuromodulator**

* R/O major motility disorder, belching syndrome and gastric emptying issue if not done already
The PPI Non-Responsive Patient - The Functional (Visceral Hypersensitivity) GERD Patient: Treatment Options

Ronnie Fass, MD  
Professor of Medicine  
Case Western Reserve University  
Chairman, Division of Gastroenterology and Hepatology  
Director, Esophageal and Swallowing center  
MetroHealth Medical Center

Consulting the Best Regarding the Lecture’s Topic
Visceral Hypersensitivity

• The perception of non-painful esophageal stimuli as being painful and the perception of painful esophageal stimuli as being more painful

Visceral hypersensitivity is a heightened conscious perception of visceral stimuli independent of the intensity

Basic Terminology

• Hyperalgesia: Increase in pain in response to normally painful stimuli
• Allodynia: Perception of pain in response to stimuli that are normally not perceived as painful
• Central hyperalgesia: Increased excitability of neurons in the CNS involved in nociceptive processing
• Peripheral hyperalgesia: Increased excitability of tissue nociceptors
Visceral Hyperalgesia

Mayer EA. Contemp Intern Med 1994;6(7):42-54

Esophageal Hypersensitivity in GERD

Hersheyviel T and Fass R. J Neurogastroenterol Motil, 2010

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Documenting Esophageal Hypersensitivity in NCCP Patients Using Balloon Distension Protocol

- Soft Elastic balloon (polyvinyl)
- Air Infused by hand held syringe (1 cc increments) at 10 cm > LES
- Main clinical outcome – Pain Threshold

Central Mechanisms That Modulate Pain Perception in GERD Patients

Anxiety/stress
Psychological comorbidity
Sleep deprivation
Attention/Expectation/Conditioning
Esophageal Hypersensitivity in Subtypes of Gastroesophageal Reflux Disease

Exposure to noxious gastric content

Barrett’s Esophagitis NERD FH


The Functional GERD Patients In The Context OF PPI Failure

- Refractory GERD (per se)
- GERD and functional gastrointestinal disorders
- Functional heartburn – Not a GERD patient!!!

**Distribution of Percent Total Time pH <4 Along the Esophagus of NERD, EE and BE Patients, using a 4-Sensor pH Probe**

Dickman *et al.* Am J Gastroenterol 2006;101:2463-2469

**Intraesophageal Distribution and Perception of Acid Reflux in Patients with Nonerosive Reflux Disease**

**NERD Patients**

<table>
<thead>
<tr>
<th>Reflux Events</th>
<th>SAR (%)</th>
<th>NSAR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 cm &lt;UES</td>
<td>120 (23)</td>
<td>393 (77)</td>
</tr>
<tr>
<td>3 cm &lt;UES</td>
<td>67 (37)</td>
<td>112 (63)</td>
</tr>
</tbody>
</table>

**Erosive Esophagitis**

<table>
<thead>
<tr>
<th>Reflux Events</th>
<th>SAR (%)</th>
<th>NSAR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 cm &lt;UES</td>
<td>59 (13)</td>
<td>387 (87)</td>
</tr>
<tr>
<td>3 cm &lt;UES</td>
<td>26 (13)</td>
<td>174 (87)</td>
</tr>
</tbody>
</table>

SAR – Symptom associated reflux
NSAR – Non-symptom associated reflux

**Proportion (%) of Symptomatic Events According to Acidity at Each Esophageal Site**

<table>
<thead>
<tr>
<th></th>
<th>All NERD</th>
<th>NERD pH+ (N=8)</th>
<th>HE (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidic reflux (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 cm above LES</td>
<td>11 ± 2</td>
<td>11 ± 3</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>15 cm above LES</td>
<td>18 ± 5*</td>
<td>17 ± 6*</td>
<td>18 ± 7*</td>
</tr>
<tr>
<td>20 cm above LES</td>
<td>25 ± 8*</td>
<td>20 ± 8*</td>
<td>30 ± 19*</td>
</tr>
</tbody>
</table>

*Weakly acidic reflux (%)*


*P<0.05 vs distal

**Correlation Between Esophageal Pain Thresholds and DeMeester Score in NERD Patients**

Approximately 86% of the patients with nonerosive reflux disease demonstrate esophageal hypersensitivity

Hobson et al. Neurogastroenterol Motil 2008;20:877-883

N=15
The Reported Rate of Symptomatic Failure in Therapeutic Trials of GERD Patients

- Nonerosive reflux disease: 40%–50%
- Erosive esophagitis: 25%–40%
- Barrett’s esophagus: 20%

PPI Failure

Fass R. Drugs 2007;67:1521-1530
Fass R. Clin Gastroenterol Hepatol 2007;6:393-400

The Functional GERD Patients

- Symptomatic patients on double dose PPI
  - Nonacid reflux: 35%
  - Acid reflux: 8%
  - Symptoms not associated with reflux: 57% = Func. HB

Mainie et al: Gut, 2006; 55:1398-1402
Comparison of Reflux Characteristics Between PPI Failure and PPI Success Patients Using A Combined pH and Billitec Testing (all $P>0.05$)

<table>
<thead>
<tr>
<th>% of patients</th>
<th>Acid reflux</th>
<th>DGER</th>
<th>Acid reflux + DGER</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI Failure (N=24)</td>
<td>None</td>
<td>Acid reflux</td>
<td>Acid reflux + DGER</td>
</tr>
<tr>
<td>PPI Success (N=23)</td>
<td>None</td>
<td>Acid reflux</td>
<td>Acid reflux + DGER</td>
</tr>
</tbody>
</table>


Comparison of PPI Responders versus Partial Responders

- No difference in the rate of acid reflux
- No difference in the pH of acid pocket
- No difference in position of acid pocket
- No difference of permeability of esophageal mucosa

Partial Responders - Increased Sensitivity to Balloon Distension

Partial Responders – More Proximal Reflux Events

Who Are The Functional GERD Patients?

Symptomatic patients on double dose PPI

- Nonacid reflux (35%)
- Acid reflux (8%)
- Symptoms not associated with reflux (57%) = Func. HB

Mainie et al: Gut, 2006; 55:1398-1402

Functional Heartburn

(Rome III Criteria)

Must include all of the following criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis:

- Burning retrosternal discomfort or pain
- Absence of evidence that gastroesophageal reflux is the cause of the symptom
- Absence of histopathology-based esophageal motility disorders
Ronnie Fass, MD, FACG

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**Functional Heartburn and Esophageal Hypersensitivity**

75% of FH

- Psychological comorbidity
- Compliance
- Improper dosing time
- Weakly acidic reflux
- Duodenogastroesophageal reflux
- Residual acid reflux
- Delayed gastric emptying
- Concomitant functional bowel disorder
- Reduced PPI bioavailability
- Rapid PPI metabolism
- PPI resistance
- Others

Maradey –Romero et al. CGH

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**Refractory GERD – A Functional Disorder?**

- Psychological comorbidity
- Compliance
- Improper dosing time
- Eosinophilic esophagitis (?)
- Weakly acidic reflux
- Duodenogastroesophageal reflux
- Residual acid reflux
- Delayed gastric emptying
- Concomitant functional bowel disorder

The Influence of Co-Morbid IBS and Psychological Disease on Response to PPI Therapy in Patients with GERD

- Overlap with functional bowel disorders
  - GERD patients with stress and/or IBS perceive their GERD-related symptoms as more severe as compared to GERD patients without IBS.
  - Treated GERD patients with stress and/or IBS tended to not achieve the same improvement in GERD-related symptoms as those without IBS.


Clinical and not Impedance/pH profile Predict Response to PPI

- No reflux pattern associated with PPI failure can be demonstrated by 24 h Impedance/pH performed off therapy
- Body mass index (BMI) < 25 kg/m2 is an important factor of inadequate response to PPI
- Functional digestive disorders are independent predictive factors of PPI failure even in patients with documented GERD

Zerbib F et al. Gut 2012
The Functional GERD Patient - Treatment

- Weakly acidic/alkaline reflux
  - TLESR reducer
  - Prokinetics
  - Endoscopic treatment
  - Ant-reflux surgery

- Residual acidic reflux
  - Pain Modulators

Pain Modulators for the Treatment of Disorders With Esophageal Hypersensitivity

**Table 2: Pain modulators for the treatment of functional esophageal disorders**

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Dose</th>
<th>Disorder</th>
<th>RCT</th>
<th>Side effects</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>50 mg/d</td>
<td>NCP</td>
<td>+</td>
<td>+/-</td>
<td>57%</td>
</tr>
<tr>
<td>Desipramine</td>
<td>10-15 mg/d</td>
<td>NCP, global</td>
<td>+/-</td>
<td>+/-</td>
<td>52%</td>
</tr>
<tr>
<td>SSRs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>50-200 mg/d</td>
<td>NCP</td>
<td>+</td>
<td>+/-</td>
<td>57%</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20 mg/d</td>
<td>SI</td>
<td>+/-</td>
<td>+/−</td>
<td>45-25%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>30-50 mg/d</td>
<td>NCP</td>
<td>+</td>
<td>+/-</td>
<td>52%</td>
</tr>
<tr>
<td>Trazodone</td>
<td>50-100 mg/d</td>
<td>NCP</td>
<td>-</td>
<td>+/−</td>
<td>50%</td>
</tr>
<tr>
<td>Other pain-modulating agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dickman R and Fass R. Neurogastroenterol Motil 2014;26:603 - 10
Pain Modulators for Esophageal Hypersensitivity

- **Antidepressants**
  - TCA’s, SSRIs, SNRIs and Trazodone
- **Adenosin agonists** (theophylline)
- **Serotonin agonists** (tegaserod)
- **Antiepileptics** (Pregabalin)
- **Peripheral neuropathy analgesics** (Gabapentin)
- In partial responders – combine with a PPI


Receptor Activity And Dosages For Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>NE</th>
<th>5-HT</th>
<th>H1</th>
<th>ACh</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>+++</td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
<td>10-50mg</td>
</tr>
<tr>
<td>Imipramine</td>
<td>++</td>
<td>++</td>
<td>++++</td>
<td>++</td>
<td>10-50mg</td>
</tr>
<tr>
<td>Desipramine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>10-50mg</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>10-50mg</td>
</tr>
<tr>
<td>Doxepine</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
<td>++</td>
<td>10-50mg</td>
</tr>
</tbody>
</table>

Tornblom H et al. Neurogastroenterol Motil 2015;27:455-467
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

Tips For TCA’s Utilization

- Start 10 mg at bedtime (improve sleep)
- Increase by 10 mg increments weekly
- Goal of treatment 30 mg–50 mg once daily
- If side effects emerge:
  - Decrease to a lower dose
  - Can switch to another TCA
- May combine with SSRIs
- Explain patient – non-mood altering doses

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

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>Citalopram 20mg once daily</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=39</td>
<td>*P=0.02</td>
<td></td>
</tr>
<tr>
<td>N=36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Viazis Am J Gastro 2012

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>

Efficacy of Venlafaxine (75 mg qhs) Vs. Placebo on the Mean Intensity Symptom Score

![Graph showing symptom intensity score over time for Venlafaxine and Placebo periods. N=43.](image)


Other Esophageal Pain Modulators

- Adenosin agonists (theophylline)
- 5-HT4 agonists (tegaserod)
- 5-HT3 antagonists (Ondansentron)
- Antiepileptics (Pregabalin)
- Peripheral neuropathy analgesics (Gabapentin)
- Somatostatin analog (Octreotide)

Comparing Omeprazole with Fluoxetine for Treatment of Patients with Heartburn and Normal Endoscopy who Failed Once Daily Proton Pump Inhibitors: Double-Blind Placebo-Controlled Trial

Ostovaneh MR et al. Neurogastroenterol Motil 2014;26:670-8

The Role of Acupuncture in Refractory GERD

Dickman R et al. Aliment Pharmacol Ther 2007; 26;1333-1334
**The Effect Of Melatonin In Functional Heartburn**

3 months, randomized, placebo-controlled trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=20</th>
<th>Patients with improvement in heartburn symptoms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin 6mg</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Nortriptyline 25mg</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>


**Hypnotherapy For Functional Heartburn**

- An open label
- weekly session of hypnotherapy X7
- 9 FH patients aged 32 – 60 years
- There was a significant decrease in visceral anxiety (p = 0.01) and symptom severity (p = 0.01)
- All Patients reported improvement in symptoms (slight to substantial)

Riehl ME et al. Dis Esoph 2015 (in press)
Always Address Psychological Co-Morbidity

* Anxiety
* Depression
* Somatization
Non-Acid Reflux: Detection, Clinical Relevance, Management

Marcelo F. Vela, MD, MSCR, FACG
Mayo Clinic
Scottsdale, AZ

GERD PATHOGENESIS

- Heartburn
- Nociceptor activation
- Injury
- Esophageal Defense Mechanisms
- LES
- Acid
MEDICAL TREATMENT: SUPPRESS GASTRIC ACID

Heartburn

Nociceptor activation

Esophageal Defense Mechanisms

Injury

LES

PPI Efficacy: Randomized Controlled Trials

Placebo

Therapeutic gain

MEDICAL TREATMENT: SUPPRESS GASTRIC ACID

Incomplete Response to PPI:
30% for heartburn
worse for other symptoms

How do we deal with these patients?
How can we improve our diagnostic and therapeutic strategy?

KEY questions:
1. Do these patients have GERD?
2. If they have GERD, what explains the lack of response?

TESTING FOR GERD: TARGETS

Reflux Monitoring
TESTING FOR GERD: REFLUX MONITORING

pH-monitoring

5 cm above LES

Is there an abnormal amount (pathological) of reflux?

Is there an association between reflux episodes and symptoms?

Purpose: answer 2 questions
WIRELESS pH MONITORING

- Improved patient comfort and acceptance
- Less restriction of diet and daily activities
- Prolonged monitoring: 48 – 96 hours
- Increased yield

CONVENTIONAL MONITORING: pH

ACID REFLUX

- In patients with ongoing symptoms despite adequate acid suppression
- Reflux mechanism not changed
- Nonacid reflux?
TESTING FOR WEAKLY ACIDIC or NONACID REFLUX

pH testing

Impedance-pH testing

ACID REFLUX
The clinical value of impedance-pH monitoring is directly related to the relevance of weakly acidic or non-acid reflux.
PATHOGENESIS OF SYMPTOMS DUE TO NONACID REFLUX

Chemoreceptors
Mechanoreceptors

Acid, hyperosmolarity
Distension

SYSTEMATIC REVIEW: ROLE OF ACID, WEAKLY ACIDIC AND WEAKLY ALKALINE REFLUX IN GERD

• 21 studies involving 664 patients
  • 374 patients on PPI / 382 patients off PPI

Boecksxtaens and Smout Aliment Pharmacol Ther 2010
SYSTEMATIC REVIEW: ROLE OF ACID, WEAKLY ACIDIC AND WEAKLY ALKALINE REFLUX IN GERD

- 21 studies involving 664 patients
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Boecksxtaens and Smout Aliment Pharmacol Ther 2010

SYSTEMATIC REVIEW: ROLE OF ACID, WEAKLY ACIDIC AND WEAKLY ALKALINE REFLUX IN GERD

- Symptom-related reflux episodes

Boecksxtaens and Smout Aliment Pharmacol Ther 2010
WEAKLY ACIDIC OR NON-ACID REFLUX: IS IT TREATABLE?

MANAGEMENT OF PERSISTENT REFLUX DESPITE PPI (ACID OR NON-ACID)

- Modulate anti-reflux barrier:
  - Peristalsis
  - Pharmacologically: TLESR inhibitor: Baclofen, others
  - Surgically: Fundoplication
  - Endoscopically: Endoscopic anti-reflux procedures (ACID)
EFFECT OF BACLOFEN ON ACID AND NONACID REFLUX

- 18 subjects with heartburn
- Randomized crossover study: baclofen vs placebo

![Graph showing the effect of baclofen on acid and nonacid reflux.](image)

Vela, Aliment Pharmacol Ther 2003

Nissen Fundoplication in Refractory GERD

- 40 patients with heartburn / regurgitation despite PPI
- Impedance-pH monitoring:
  - on PPI before surgery
  - off PPI 3 months after fundoplication

![Graphs showing esophageal acid exposure time and number of reflux episodes.](image)

Frazzoni et al. Dig Dis Sci 2011;56:1099

Hiatus hernia: 66%
History esophagitis: 50%
Nissen Fundoplication in Refractory GERD

- 3-year follow-up in 38 patients recently published
  - Good symptom control in 34 of 38
  - Reflux parameters improved

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before surgery</th>
<th>After surgery</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>LES tone, mmHg</td>
<td>13 (8–20)</td>
<td>19 (14–25)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total refluxes</td>
<td>68 (45–94)</td>
<td>8 (4–17)</td>
<td>0.001</td>
</tr>
<tr>
<td>Abnormal %EAET</td>
<td>6 (16 %)</td>
<td>3 (8 %)</td>
<td>0.480</td>
</tr>
</tbody>
</table>

Frazzoni Surg Endosc 2013

pH versus Impedance-pH prior to Fundoplication in Patients with Extraesophageal Reflux

- 27 patients with objective evidence of GERD underwent fundoplication
- Prior to surgery: 48-h wireless pH OFF PPI
  24-h impedance-pH ON PPI
- 59% at least partial improvement of extraesophageal symptom on f-u

Predictors of symptomatic improvement on multivariate model:
- Concomitant heartburn
- % time pH <4 greater than 12%

Factors that did NOT predict improvement:
- no. reflux episodes by impedance
- SI/SAP during 48-h pH or 24-h impedance-pH study
- % time pH <4 greater than 5%

Francis Laryngoscope 2011
ISSUES AND UNANSWERED QUESTIONS

- No controlled studies of surgery for nonacid or weakly acidic reflux
- How best to define an abnormal test?
- What parameters predict response to therapy?

PERSISTENT SYMPTOMS DESPITE ACID SUPPRESSION
SUMMARY

• 30-40% patients: incomplete control on PPI

• Ongoing symptoms: acid GER / nonacid GER / no GER
  • Impedance-pH superior for testing on medication
SUMMARY

• 30-40% patients: incomplete control on PPI

• Ongoing symptoms: acid GER / nonacid GER / no GER
  • Impedance-pH superior for testing on medication

• Nonacid reflux
  • Measureable by impedance-pH
  • Responsible for symptoms in some patients
  • Responds to treatment – RCT needed

• Stop PPIs if there is no evidence of GERD
SUMMARY

• 30-40% patients: incomplete control on PPI

• Ongoing symptoms: acid GER / nonacid GER / no GER
  • Impedance-pH superior for testing on medication

• Nonacid reflux
  • Measureable by impedance-pH
  • Responsible for symptoms in some patients
  • Responds to treatment – RCT needed

• Stop PPIs if there is no evidence of GERD

Thank you
Symptoms not due to reflux

Nonacid reflux

Acid reflux

Abnormal: GERD

Normal: GERD

No GERD

MANOMETRY

REFLUX MONITORING

Low pre test probability of GERD

High pre test probability of GERD

Test off medication with pH or impedance

Test on medication with impedance

Normal

Abnormal: GERD

Normal

Symptoms not due to reflux

Nonacid reflux

Acid reflux

Escalate Therapy