Refractory GERD

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Objectives

• Define the terminology associated with refractory GERD and PPI failure
• Identify predictors of response to increasing acid suppression in refractory patients
• Characterize the role of visceral hypersensitivity in refractory NERD patients
• Discuss non-acid blocking therapy in GERD
PPIs are the most effective drugs for the initial treatment of GERD

Chiba et al. Gastroenterology 1997

5-way cross over trial of PPIs (mean hours intragastric pH >4)

**What about BID**  
**Intragastric pH Control**

**Mean Intragastric pH >4 on day 5; Corrected data**

<table>
<thead>
<tr>
<th>Medication Dosing</th>
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<tr>
<td>40 mg qd</td>
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<tr>
<td>40 mg BID</td>
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- 15.3 hours
- 19.46 hours

**Acid Suppression:**  
**Is there room for Improvement?**

- **Duration of Action (pH >4.0 gastric pH monitoring)**
  - 15 hours  Best PPI qd
  - 19 hours  Best PPI BID

- **Onset of Action**
  - Most PPIs take 3-5 days to reach steady state
  - Limits efficacy for “on-demand”

- **Need for taking prior to meals**
  - Except dexlansoprazole and IR omeprazole

**References:**

Based on the available RCTs you would expect refractory GERD after once daily PPI:

- Esophagitis does not heal in 15-20% of severe cases (LA C or D)
- Esophagitis recurs in 10-30% of patients on maintenance therapy
- Symptoms continue in
  - 20-30% of esophagitis patients despite healing
  - Up to 40% of NERD patients

How should we define response?

- Complete response
  - Symptoms are controlled satisfactorily
- Partial response
  - Symptoms improve, but not satisfactorily and usually get worse if PPI is stopped*
- Non response
  - Symptoms do not improve and do not worsen when PPI stopped*

*Issues of rebound hyperacidity need to be considered
BID PPI (or going to stronger agent)

- Complete response
  - No need, may want to seek “lowest effective dose”
- Partial response
  - Reasonable to increase acid suppression, but if no improvement, cut back to qd
  - Role for pH testing if response equivocal?
- Non response
  - Unlikely to respond
  - Better to stop and do pH testing
  - *Issues of rebound hyperacidity need to be considered

Use of BID PPI-Additional Thoughts

- No clear data from RCT to support routine BID
- No reason to use less or more than typical dose
- Probably little effect of going higher than a strong PPI BID
- Second dose prior to dinner except for dexlansoprazole and IR-OME
- In general, BID omeprazole provides similar day and night control when compared to even the newest PPIs given once daily
- Controversial Issues
  - Nocturnal H2RA or Prokinetic
  - Would a second dose of PPI beat placebo?
  - Does switching PPI help?
  - Increased complications with higher doses
Are PPI safe?

- Decreased calcium absorption and increased risk of fracture
- Decline in vitamin B12 stores
- Decline in serum magnesium
- Increased risk of *Clostridium difficile* infection
- Increased risk of both community and hospital acquired pneumonia
- Small bowel bacterial overgrowth
- Increased risk of other enteric infection
- Drug interactions, most importantly to the antiplatelet drug clopidogrel
- Increased risk of chronic kidney disease
- Increased rate of dementia in PPI users

Guidance from ACG guidelines

- Decreased calcium absorption and increased risk of fracture
  - Patients with known osteoporosis can remain on PPI therapy. Concern for hip fractures and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture.
- Increased risk of *Clostridium difficile* infection
  - PPI therapy can be a risk factor for *Clostridium difficile* infection, and should be used with care in patients at risk
- Increased risk of both community and hospital acquired pneumonia
  - Short-term PPI usage may increase the risk of community-acquired pneumonia. The risk does not appear elevated in long-term users.
- Drug interactions, most importantly to the antiplatelet drug clopidogrel
  - PPI therapy does not need to be altered in concomitant clopidogrel users as there does not appear to be an increased risk for adverse cardiovascular events.
Other Associations

- Decline in vitamin B12 stores
  - If significant can take many years. B12 pill is all that is needed
- Decline in serum magnesium
  - Watch for this, particularly if potassium low and other CV issues
- Small bowel bacterial overgrowth
  - Not a lot of data, but makes sense
  - ?Probiotics or breath testing?
- Increased risk of other enteric infection
  - Traveler’s diarrhea
- Increased risk of kidney disease
  - Small increase in both acute and chronic

PPI may worsen NSAID small bowel injury
CGH June 2016

![Graph showing comparison between COX-2 SI and COX-2 SI + PPI groups in jejunum and ileum](image)
Increased rate of dementia in PPI users

Is there science behind these potential complications?

- **Proton Pump Inhibitors Accelerate Endothelial Senescence**  
  – *Circulation Research 2016*

- **The proton-pump inhibitor lansoprazole enhances amyloid beta production**  
  – *PLoS One 2013*

- **An Unexpected Effect of Proton Pump Inhibitors: Elevation of the Cardiovascular Risk Factor ADMA**  
  – *Circulation 2013*
What is the role of visceral hypersensitivity in GERD?

Increased Esophageal Sensitivity to Acid and Saline in Patients With Nonerosive Gastro-esophageal Reflux Disease
JCG 2006;40:891-5
The Effect of Auditory Stress on Perception of Intraesophageal Acid in Patients With Gastroesophageal Reflux Disease

Fass et al. Gastroenterology 2008

Loss of Sleep Worsens GERD Symptoms

Gastroenterology 2007;133:1787-95
Alternatives to Acid Suppression

Prokinetics and GERD-1995

- The pathogenesis of GERD is related to defects in esophagogastric motility
- Ideal pharmacological therapy would correct these defects, making suppression of normal amounts of gastric acid unnecessary
- Results with the available drugs have been disappointing

DeVault and Castell ACG guidelines 1995
Baclofen Versus Placebo: Impedance Parameters in GERD


Arbaclofen Placarbil Monotherapy Decreases GERD Symptoms in Subjects with Previous PPI Therapy

- Well tolerated baclofen pro-drug
- Improved symptoms in patients who had been treated with PPIs in the past.
- 30 mg BID produced complete relief of symptoms in 60% in PPI experienced patients
- Other agents are being studied as either monotherapy or perhaps adjuncts to partial PPI responders.
- *Phase II trial as add-on to PPI yielded no benefit and development was halted!*
Prokinetics

- Available agents have low efficacy and poor side effect profile
- Most “new” agents are failing
  - Baclofen like agents
    - Efficacy has been poor and reaching market is questionable for most
  - GABA-B agonist (lesogaberan)
    - Poor efficacy and elevated LFTs with some agents
- Any “new” prokinetic will likely have modest efficacy and find a place as an add-on to PPI if at all

Diet and Lifestyle Modifications

- Diet: avoid acidic/irritating foods or foods that can cause acid reflux
- Stop smoking
- Avoid coffee, tea, and caffeinated beverages
- Decrease alcohol consumption
- Elevate head of bed
- Avoid eating within 3 hours before bedtime
- WEIGHT LOSS!!!!!
Predictors of Outcome of Antireflux Surgery

- 100 consecutive patients undergoing laparoscopic antireflux surgery performed by 2 surgeons
- Surgical success rate at follow-up: 91% (average follow-up, 15 months)
- Predictors of successful surgery
  - Age <50 years
  - Present with typical GERD symptoms
  - Complete resolution of symptoms with acid-suppression therapy

N = 100.
Symptom Response after Laparoscopic Antireflux Surgery

Heartburn: 93%
Laryngeal: 78%
Pulmonary: 58%
Chest Pain: 48%

Magnetic Sphincter-Linx
Other potential tests

- **Barium**
  - Hiatal hernia size
  - Otherwise rarely helpful (unless dysphagia)
- **Esophageal Biopsy to rule out eosinophilic esophagitis**
  - Utility in patients with normal appearance and no dysphagia is unknown
- **Gastric emptying test**
  - Generally avoid except when patient has suggestive symptoms
- **Esophageal Manometry**
  - Preop test
  - Reasonable to do in conjunction with pH test
    - Localize LES
    - Evaluate peristalsis
Approach to Refractory GERD

• Make sure patient has GERD
  – Esophagitis LA-B or greater
  – Long segment BE
  – Positive pH test
• Look for alternative or other worsening factors
  – BMI
  – Rumination
  – Other motility disorders
    • Gastroparesis
    • Achalasia
  – Dyspepsia
  – Eosinophilic Esophagitis
• Optimize medical and lifestyle therapy
• Refractory regurgitation responds to surgery
  – Beware of other “refractory” symptoms

Thank you!