Managing GERD: Beyond PPIs

ACG/VGS/ODSGNA Regional Postgraduate Course
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Agenda

• Scope of the Problem
• Non-PPI Medical Therapy
• Surgical Alternatives
• Endosurgical Options
• Conclusions
Gastroesophageal Reflux Disease (GERD)

Definition: Symptoms and/or tissue damage secondary to reflux of normal gastric contents

Not all reflux is acid reflux!!!
GERD Pathogenesis

- Esophageal causes
  - Reduced saliva (e.g. anticholinergic medications)
  - Reduced peristalsis (e.g. scleroderma)
  - Lack of gravity (e.g. post-operative patient)
  - Decreased mucosal resistance due to reduced secretion from esophageal submucosal glands
- Lower esophageal sphincter dysfunction
  - Inappropriate and prolonged LES relaxations
  - Presence of a hiatal hernia
  - Weak LES (e.g. old age, scleroderma, medications)
- Gastric Causes
  - Slow gastric emptying
  - Excess acid production
  - Duodenogastric (bile) reflux

What are the pathogenic factors in reflux esophagitis?

- Volume of refluxed fluid
- Duration of reflux
- Type of refluxed fluid
- Clearing mechanisms
- Hiatal hernia
Normal Anatomy Prevents GERD

- Lower Esophageal Sphincter (LES)
  - Serves to constrict lumen in steady state
  - Relaxes to allow swallowing

- Gastroesophageal Flap Valve (GEV)
  - 180° musculo-mucosal flap valve, maintains closure against lesser curve of stomach
  - Valve responsive to intragastric pressure
  - Occludes esophagus to prevent reflux

Effect of Hiatal Hernia

- LES and diaphragm now separated
- Acid Reservoir
Why Change From PPI?

- Intolerance of PPIs
- Incomplete relief of symptoms
- Refractory acid reflux on quantitative testing
- Patient concerns regarding adverse effects of PPI use
  - Osteoporosis/hip fracture
  - Reduced absorption of nutrients/other medications
  - Immune system health/risk of *C. difficile* colitis
  - Renal insufficiency
  - Dementia

ACG Guidelines 2013

- Switching PPIs can be considered in the setting of side effects. (Conditional recommendation, low level of evidence)
- 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. (Strong recommendation, moderate level of evidence)
- PPI therapy can be a risk factor for *Clostridium difficile* infection and should be used with care in patients at risk. (Strong recommendation, moderate level of evidence)
- Short-term PPI usage may increase the risk of community acquired pneumonia. The risk does not appear elevated in long-term users. (Conditional recommendation, moderate level of evidence)
- PPI therapy does not need to be altered in concomitant clopidogrel users as clinical data does not support an increased risk for adverse cardiovascular events. (Strong recommendation, high level of evidence)

Non-PPI Medical Therapy

Dietary & Lifestyle Modifications

From the ACG Guidelines:

• Weight loss is recommended for GERD patients who are overweight or have had recent weight gain. (Conditional recommendation, moderate level of evidence)

• Head of bed elevation and avoidance of meals 2–3 hours before bedtime should be recommended for patients with nocturnal GERD. (Conditional recommendation, low level of evidence)

• Routine global elimination of food that can trigger reflux (including chocolate, caffeine, alcohol, acidic and/or spicy foods) is not recommended in the treatment of GERD. (Conditional recommendation, low level of evidence)

• Tobacco and alcohol cessation have not been shown to change either GERD symptoms or esophageal pH. 1–3

Therapeutic Modalities to Affect Gastric Acid Secretion

Antacids & Topicals

- **Antacids:**
  - Examples: calcium carbonate, aluminum hydroxide, magnesium trisilicate
  - Do not prevent GERD, only treat its symptoms by neutralizing gastric pH which decreases the acidity of any refluxate
  - Rapid onset of action (<5 minutes) but short duration of efficacy (<1 hour)

- **Sucralfate:**
  - Available in both tablet and suspension form
  - Adheres to esophageal wall and protects from peptic injury via unknown mechanism
  - Short duration of action, limited efficacy compared to PPIs
  - ACG Guidelines: There is no role for sucralfate in the non-pregnant GERD patient. (Conditional recommendation, moderate level of evidence)

- **Sodium alginate:**
  - Derived from seaweed
  - Forms a viscous gum which floats on the surface of gastric contents, reducing the postprandial “acid pocket” in the proximal stomach
  - Studies suggest it may be beneficial, especially with mild post-prandial symptoms

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Prokinetics & Other Non-Acid Reducers

- **Prokinetics**
  - Examples include metoclopramide and domperidone
  - Can increase lower esophageal sphincter pressures, improve peristalsis in addition to promoting gastric emptying
  - Metoclopramide CNS-based side effects include depression and tardive dyskinesia (black box warning from FDA)
  - Domperidone does not penetrate the blood-brain barrier but does carry a risk of ventricular arrhythmia; also requires and IDA from the FDA

- **Baclofen**
  - GABA(b) agonist shown to decrease TLESRs and reflux events

- **ACG Guidelines:**
  - Therapy for GERD other than acid suppression, including prokinetic therapy and/or baclofen, should not be used in GERD patients without diagnostic evaluation. (Conditional recommendation, moderate level of evidence)

1 Champion MC. *Can J Gastroenterol* 1997; 11 (Suppl B): 55B – 65B.

H₂Receptor Antagonists (H₂RAs)

- Act on type 2 histamine receptors on the basal side of the parietal cell
- Faster onset of action than PPIs, but shorter half life
- Dosing for mild GERD generally is PRN or BID
- Studies have shown superiority of PPIs over H₂RAs for relief of heartburn in NERD patients (7 trials with RR of continued heartburn 0.37 for PPIs, 0.77 for H₂RAs, 95% CI 0.60-0.73) ¹

- **ACG Guidelines:**
  - H₂RA therapy can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief. (Conditional recommendation, moderate level of evidence).
  - Bedtime H₂RA therapy can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed, but may be associated with the development of tachyphylaxis after several weeks of use. (Conditional recommendation, low level of evidence)

Long-Term Esophagitis Remission

Surgical Alternatives

Indications for Surgery in 2016

• Healthy GERD patient controlled on PPIs
  – Cost of continuing lifelong PPI treatment
  – Compliance with lifelong medication
  – Ongoing side effects with current use
  – Fear of side-effects of long term use
• Esophagitis refractory to medical therapy
• Volume regurgitation and aspiration symptoms not controlled on PPIs
  – Large hiatal hernia
• Atypical GERD symptoms relieved on PPIs
• Persistent symptoms documented to be caused by refractory GERD (pH/impedance testing)
Nissen Fundoplication

- 360 degree wrap of fundus around the esophago-gastric junction to bolster the lower esophageal sphincter
- Mostly performed laparoscopically
- 10 year follow-up of VA study ¹
  - 62% of Nissens using medical therapy, vs. 92% of non-surgical patients
- 12 year follow-up in separate study ²
  - 53% of Nissens in remission, vs. 45% of PPIs
- Most common side effects:
  - Gas-bloat (up to 15-20% of patients)
  - Dysphagia (generally transient but not always)

Other Surgical Options

- **Toupet Fundoplication:**
  - 270-300 degree wrap of fundus around the esophago-gastric junction
  - Thought to generate less dysphagia
  - Preferred approach for refractory GERD in the setting of known esophageal dysmotility

- **Roux-en-Y Gastric Bypass:**
  - Creates physical separation between oxyntic mucosa of the stomach and the esophagus
  - Facilitates weight loss along with decreased acid exposure to the distal esophagus
  - May be the preferred option for long-term GERD management in obese patients

Magnetic Sphincter Augmentation

- Ring of titanium beads encasing magnetic cores placed surgically at the level of the lower esophageal sphincter
- Size of ring (number of beads) selected based on esophageal measurement at time of placement
- Magnetic forces augment LES pressure to approximately 15 mmHg
- Passage of a bolus through the esophago-gastric junction allows for dynamic opening of the ring, as pressure generated by the bolus overcomes that of the beads
- Goal of this system is to allow for pressure-induced opening of the LES, which is not possible after suturing during a fundoplication (belching and vomiting possible, less dysphagia, etc.)
- Data now available on 85 patients at 5 years
Results at 5 Years

ACG Guidelines

• **Surgical therapy is a treatment option** for long-term therapy in GERD patients. (Strong recommendation, high level of evidence)

• Surgical therapy **is as effective as medical therapy** for **carefully selected patients** with chronic GERD when performed by an experienced surgeon. (Strong recommendation, high level of evidence)

• Surgical therapy is generally **not recommended** in patients who **do not respond to PPI** therapy. (Strong recommendation, high level of evidence)

ACG Guidelines II

• Preoperative ambulatory **pH monitoring is mandatory** in patients **without evidence of erosive esophagitis**. **All patients should undergo preoperative manometry** to rule out achalasia or scleroderma-like esophagus. (Strong recommendation, moderate level of evidence)

• **Obese patients** contemplating surgical therapy for GERD should be **considered for bariatric surgery**. Gastric bypass would be the preferred operation in these patients (Conditional recommendation, moderate level of evidence)
Electrical Stimulation Therapy of LES

- Implantation performed with laparoscopy
- 2 small leads placed on LES
- Neurostimulator connected to leads sends mild electrical signals throughout the day (not generally sensed by patients) to improve LES function
- 2 year data of multi-center trial
  - 21 patients with GERD partially responsive to GERD and hiatal hernia 3 cm long or less made interim analysis
  - Median GERD-HRQL scores dropped from 9 to 0 (comparing current to pre-EST scores on and off PPI)
  - 16/21 patients totally off PPI
  - 2/21 patients using PPI daily
  - Median 24 hour distal acid exposure was 10% at baseline and 4% (per protocol, p < 0.001)
  - No serious adverse events reported

Radiofrequency Energy

- Ablation performed at 6 levels in the region of the esophagogastric junction
- Outpatient endoscopic procedure
- Does not preclude use of other anti-reflux measures in the future

RF: Potential Mechanism of Action

- Increases gastric yield pressure in pig model vs. control
  
- Reduces transient LES relaxations (TLESRs) when applied to the gastric cardia in dogs

- Randomized control study of 22 patients:
  - RFA decreased GEJ compliance compared to sham patients
  - Use of sildenafil (smooth muscle relaxant) 3 months after RFA restored normal compliance, suggesting fibrosis is not the driving force behind decreased compliance

References:

RF: Meta-analysis of 1,441 Patients

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RF: Durability of Response

- 99 study patients with refractory GERD followed for 10 years
- PPI needs: 64% no longer required the same dose of PPI as pre-RF, and 41% remained off PPIs completely
- Normalization of GERD-HRQL scores (primary endpoint) in 70% of patients
- Response rate in patients with variant anatomy and prior anti-reflux surgery was the same as those with standard anatomy
RF: Endorsed by SAGES

Endoluminal Treatments for Gastroesophageal Reflux Disease (GERD)

Edward D. Auyang, Patrice Carter, Thomas Rauth, Robert D. Fanelli and the SAGES Guidelines Committee

Recommendation:
Stretta is considered appropriate therapy for patients being treated for GERD who are 18 years of age or older, who have had symptoms of heartburn, regurgitation, or both for 6 months or more, who have been partially or completely responsive to anti-secretory pharmacologic therapy, and who have declined laparoscopic fundoplication.

Quality of Evidence: (++++). GRADE Recommendation: Strong


Transoral Incisionless Fundoplication (TIF)

- H-shaped fasteners applied for full-thickness plication to recreate the gastroesophageal flap valve
- Final result is a 2-3 cm long valve of approximately 270 degrees
- Requires hiatal hernia of no more than 2 cm pre-TIF

Gastroenterology 2015
TIF: Improvement Through 12 Months

- Randomized control trial of high-dose PPIs vs. TIF
- PPI patients crossed over to have TIF after 6 months
- 39 TIF and 21 crossover patients studied
- Significant improvement in symptom elimination (p < 0.001) and healing of esophagitis (p < 0.018)

TIF: Durability Through 24 Months

- Prospective U.S. Registry to assess 2 year outcomes
- Primary endpoint: symptom assessment
- 108 patients completed study


Ultrasonic Surgical Endostapler

- Disposable endoscopic system contains ultrasound sensor to facilitate firing of 3 rounds of 4.8 mm titanium staples
- End result is a 150-180 degree anterior fundoplication

Still images from Dr. Ali Lankarani via https://youtu.be/fsuFKt5MILc
Ultrasonic Endostapler: Key Data

- 66 patients in multi-center trial (6 month data) \(^1\)
  - 65% of patients off PPI
  - 85% either off PPI or with 50%+ reduction in PPI use
- 34 patients in multi-center trial followed at least 4 years \(^2\)
  - 69% remain off PPI at conclusion of study period

Endotherapy In 2016

- 2013 ACG Guidelines: 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)

  - Why?
    - 2013 already was a long time ago!
    - Relatively small sample sizes in clinical trials to date
    - Durability data, other than with radiofrequency, is not yet available

  - Worth considering these alternatives when patient comorbidities and/or preferences preclude use of surgical techniques

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Conclusions

• PPIs remain the most potent acid-reducing agent in our medical arsenal for treating GERD; switching to another medication is unlikely to improve control of reflux (acid or non-acid)

• If a patient continues to be symptomatic despite PPI therapy, ensure they are taking their medication correctly, then confirm refractory GERD with 24 hour pH/impedance testing

• Prior to any mechanical intervention for reflux, check esophageal function with manometry to exclude dysmotility

• Surgical intervention remains the best option for improving the mechanical barrier to gastroesophageal reflux, as new options show promise as alternatives to Nissen fundoplication

• Endoscopic techniques to bolster the anti-reflux barrier show promise, with sample size and durability data forthcoming