GERD and Barrett’s Esophagus
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Disclosures
- Spouse is a physician employed by Boston Scientific Corporation
- The content of this lecture equitably discusses products of multiple companies as they pertain to the subject matter

Gastroesophageal Reflux Disease
- The most common GI diagnosis in outpatient MD office visits
- Most patients with symptoms of GERD do not have identifiable esophagitis on endoscopy
- Prevalence 10 – 20 % (once weekly symptoms)
- May underestimate the true prevalence given that a significant proportion of patients with esophagitis and Barrett’s esophagus have no reflux symptoms

Gastroesophageal Reflux Disease
- Symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus (ACG, 2005)
- Primary symptoms: heartburn, regurgitation
- Esophageal vs. extra-esophageal
- Primary finding: reflux esophagitis

Gastroesophageal Reflux Disease
- Some degree of reflux of gastric contents is normal in all people
  - Generally post-prandial, brief, does not cause symptoms and rarely occurs during sleep
  - Reflux becomes GERD when symptoms are frequent or there is damage to the lining
  - GERD is not a result of increased acid production, but rather increased exposure of the esophagus to acid due to reflux, impaired emptying of the esophagus, diminished salivation

Gastroesophageal Reflux Disease
Mechanisms of Reflux
- Transient LES relaxations
  - Not associated with swallow, longer duration
  - Not accompanied by a peristaltic wave
- Low pressure LES
  - As a result of other factors (mint, caffeine, mediations, etc.)
- Disruption of the normal LES (hiatal hernia)
GERD - Mechanisms

- α-Adrenergic antagonists
- Anti-cholinergics
- Antihistamines
- β-adrenergic agonists, including inhalers
- Calcium channel blockers
- Diazepam
- Estrogens
- Narcotics
- Progesterone
- Theophylline
- Tri-cyclic antidepressants

GERD - Montreal definition

GERD - Treatment

- Lifestyle modifications
  - Raise the head of the bed at least 6 inches
  - Dietary modifications (caffeine, mint, alcohol, chocolate, etc.)
  - Weight loss and avoiding tight fitting garments
  - Minimize alcohol and smoking cessation

GERD - Treatment

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RF Harvey, et al. Lancet 1987
GERD - Treatment

**Anti-secretory therapy**
- PPIs are superior to H2RAs which are superior to placebo in healing esophagitis and resolving GERD symptoms
- For esophagitis:
  - PPIs are superior to placebo: 83% vs. 48%, NNT 1.7
  - PPIs are superior to H2RAs: 84% vs. 53%
- No difference in efficacy among PPIs
- Use of twice daily PPI is based on expert opinion
  

**Adjunctive therapy**
- Insufficient evidence to support nocturnal H2RA in addition to twice daily PPI
- Recommend against the use of metoclopramide for GERD symptoms
- Recommend against the acute use of anti-secretory therapy for extra-esophageal symptoms without concomitant esophageal syndrome
  

GERD – Treatment Side-effects

- Pneumonia
- Acid protects esophageal colonization
- C.diff diarrhea
- Hyperacidity
  - Withdrawal reflux
- B2 Malabsorption
- Hip fracture
  - Osteoclast activity
  - Calcium absorption
- Hypomagnesemia
  - Reduced absorption
  - Muscle spasm, arrhythmias, seizures
- Plavix and Omeprazole
  - Hepatic clearance

GERD – Role of endoscopy

- Alarm symptoms – are not a good diagnostic tool in general
- Significant dysphagia, weight loss and epigastric mass are each somewhat predictive of finding a malignancy on EGD
  
- AGA technical review identifies significant dysphagia and lack of response to an empiric trial of PPIs as indications for endoscopy (Grade B)
- Low threshold for biopsies to assess for Eosinophilic esophagitis (at least 5, multiple levels)

GERD – Supplemental testing

- Manometry for patients who have not responded to PPI and have a normal endoscopy
- pH testing (catheter or wireless) for those patients who have not responded to PPI, have a normal EGD and have no major abnormality on manometry
  - PPI therapy held for one week
  - Wireless 48 hour recording has higher sensitivity and accuracy than catheter-based testing

GERD Treatment – “Atypical” symptoms

- Reflux chest pain
  - Once cardiac causes have been assessed, empiric twice daily PPI for 4 weeks is cost effective and 80% sensitive in diagnosing GERD as the cause
  
- Cough, asthma, laryngitis
  - PPI’s have demonstrated efficacy only in patients who have concurrent esophageal symptoms
GERD Treatment - Endoscopy

- Not currently recommended
  - "Burn it" - Stretta (radiofrequency)
  - "Tie it" – EndoCinch, NDO Plicator, EsophyX.
  - "Stuff it" - Enteryx

GERD Treatment - Surgery

- Laparoscopic Nissen fundoplication
  - Extremely low mortality and low morbidity
  - Effective (> 90% response rate initially, decreases to 70-80% in 3-5 year follow-up)
  - Gas-bloat, inability to belch and dysphagia is seen in a significant number of patients post-operatively
  - Some fraction (varies greatly from study to study) will be back on PPIs 2-5 years post-operatively

Question:

- 43 y/o male patient presents for follow-up office visit for heartburn. He has been compliant with lifestyle modifications and omeprazole once daily in the morning 30 minutes before breakfast. His symptoms are well controlled during the day, but recur at night. What is the next step in management?
  - A. Start ranitidine 150 mg at bedtime
  - B. Refer for upper endoscopy
  - C. Start metoclopramide 10 mg
  - D. Refer for manometry testing
  - E. Increase omeprazole dose to 20 mg twice daily

Barrett’s esophagus

- Replacement of the normal squamous epithelium of the esophagus with metaplastic columnar epithelium and predisposes to adenocarcinoma
- Occurs as a result of chronic inflammation from gastroesophageal reflux disease (GERD)
- Progression to carcinoma generally occurs in a step-wise fashion from no dysplasia, low-grade dysplasia and high-grade dysplasia
Barrett’s esophagus – Epithelial Type

1. gastric fundic-type epithelium that has mucus-secreting cells, parietal cells, and chief cells

2. a cardia-type (junctional-type) epithelium composed almost exclusively of mucus-secreting cells

3. intestinal-type epithelium (specialized intestinal metaplasia) with goblet cells

Barrett’s esophagus – Clinical Classification

- Short-segment Barrett’s – less than 3 cm
  - Lower incidence of dysplasia

- Long-segment Barrett’s – greater than 3 cm
  - Higher risk of dysplasia and progression to adenocarcinoma

- Limitations – limited prospective data

Barrett’s esophagus

- Prague Classification
  - C & M
  - Circumferential extent of Barrett’s
  - Maximal extent of Barrett’s

Screening

- AGA, ACG and ASGE have somewhat different guidelines for screening.

- ACG and AGA’s most recent guidelines acknowledge the controversy in screening stating that the highest yield is in screening those with chronic GERD over age 50

- If Barrett’s is identified on screening, repeat in one year then every 3-5 years if no dysplasia

Surveillance

- Low-grade dysplasia annual surveillance

- High-grade dysplasia ablative therapies vs. surgery

- No prospective data on the survival benefit of surveillance
Risk of progression

• Risk of Cancer
  • Prior data: 0.2 to 2.0% absolute risk per year in patients with nondysplastic BE
  • Sikkema 2010 (Meta-analysis)
    • 51 studies
    • Incidence: 6.3 / 1000p-y
  • Hvid-Jensen 2011 (Population-based cohort)
    • 11,028 patients
    • Incidence: 1.2 / 1000p-y
    • Rises with dysplasia (5.0 / 1000 p-y for LGD)
    • 0.12% absolute risk per year

Low-grade dysplasia in Barrett’s

• "Treatment" is generally management of GERD symptoms and endoscopic surveillance
• Emerging data and expert opinion regarding radio-frequency ablation (BARRYX) for LGD
• Multi-center sham controlled trial of 64 patients demonstrated 90% eradication of dysplasia compared with 23% in the sham group
  
  NJ Shaheen, et al. NEJM 2009

Biomarkers of disease

• The variability of inter-observer agreement for the diagnosis of dysplasia has lead to the study of biomarkers as indicators of malignant potential
• Multiple stains and panels have been studied
• Promising markers include aneuploidy/tetraploidy as a marker of genomic instability, loss of heterozygosity (LOH) at 17p, marker panels
• No validated prospective studies as of yet
• Role may be in risk stratification of those with no dysplasia/LGD or indefinite

High-grade dysplasia in Barrett’s

• Esophagectomy
  • High morbidity and mortality
• Ablation
  • Cryotherapy
  • Photodynamic therapy
  • Radiofrequency ablation
• Endoscopic mucosal resection (EMR)

Ablation of HGD in Barrett’s

• Cryotherapy
  • Cold Nitrogen gas applied by spray catheter to freeze tissue
  • 87% eradication of dysplasia
  • 5% complication rate (stricture, severe chest pain)
  • 3% buried glands
  • Insufficient data for firm recommendations

Ablation of HGD in Barrett’s

• Photodynamic Therapy
  • Photosensitizer is preferentially taken up in neoplastic cells and produces a cytotoxic effect mediated by oxygen when the tissue is exposed to correct wavelength of light
  • Moderate risk of stricture and residual dysplasia
  • Risk of photo-injury for up to 30 days

Shaheen NJ, et al. Gastrointest Endosc. 2010
Ablation of HGD in Barrett’s
- Radiofrequency (BARRX)
  - Bipolar electrode array generates heat to “burn” < 1 mm depth

RFA of High-grade dysplasia
- Randomized, sham controlled trials have demonstrated excellent efficacy
- HGD: resolution of Barrett’s in 67 - 81%
  resolution of dysplasia in 79 – 100%
- Molecular markers of Barrett’s (Ki67, p53) are also lost after RFA
- Most common complication is stricture formation (6%) which resolves with dilation and more likely seen in patients with prior EMR

RFA of Low-grade dysplasia
- Excellent results in randomized trials > 90% eradication
- Risk / benefit analysis
- “Buried glands”
  - Unknown risk
  - Can be seen in regression of LGD with PPI as well
- Many authors now favor RFA of LGD

RFA of non-dysplastic Barrett’s
- Highly effective: 97% eradication of Barrett’s when the 360 device is followed by the 90 device for residual areas of metaplasia (70% for 360 alone in one session)
- Risk of progression of non-dysplastic Barrett’s is quite low and likely does not justify the cost / risk of RFA
- Some sub-groups may benefit – Barrett’s at a young age or family history
Endoscopic Mucosal Resection (EMR) for HGD and superficial Ca

- Can be diagnostic and therapeutic
- Often utilized in combination with ablative techniques
- Essential for removal of nodules when RFA is planned

EMR - Complications

- **Bleeding**
  - Incidence varies between studies; immediate hemorrhage often endoscopically treatable
- **Perforation**
  - Thought to be 1%
- **Stricture**
  - Risk increases with % circumference resected and length of resection

Question:

- Your long term patient, a 55 y/o male with well controlled HTN and mild hyperlipidemia, was told he has Barrett’s esophagus on a recent upper endoscopy done for longstanding GERD symptoms. He is anxious about this diagnosis and has searched the internet finding high rates of progression to cancer. What would you advise?

  A. Annual endoscopy for surveillance indefinitely
  B. Refer to a specialty center for radiofrequency ablation (RFA)
  C. Omeprazole 40 mg twice daily
  D. Reassurance, lifestyle modification, once daily PPI, surveillance endoscopy in one year then every 3-5 years
  E. Refer to a specialty center for manometry testing

Summary

- **GERD**
  - Multiple mechanisms can contribute to GERD including medications, foods and weight gain
  - PPI medications are more effective than H2RA medications
  - PPI medications are effective for extra-esophageal symptoms in those who also have esophageal symptoms
- **Barrett’s esophagus**
  - Much lower esophageal cancer incidence in patients with Barrett’s esophagus than was thought (0.12% / year)
  - Screening and Surveillance recommendations vary, but all advise screening in at risk patients and surveillance once Barrett’s is identified
  - New endoscopic treatments for high-grade dysplasia are highly effective and are an alternative to esophagectomy