GERD: Who and When to Treat

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Speaker disclosure

- I do not have any relevant commercial relationships to disclose.
- I will not discuss off-label or unapproved usage.

Objectives

- Recognize the various clinical presentations of GERD including Barrett’s esophagus
- Consider if, when and how often endoscopic surveillance should be done
- Describe the role of radio frequency ablation (RFA) in the treatment of Barrett’s esophagus
GERD: Diagnosis and Management
- Symptoms and epidemiology
- Diagnosis
- Management
  - PPI's
  - Surgical management
  - Refractory GERD
  - Extraesophageal manifestations
  - Complications
- Barrett's esophagus
  - Natural history
  - Endoscopic surveillance
  - Management of dysplasia and intramucosal adenocarcinoma

GERD: Epidemiology
- Prevalence of GERD is 10-20% (based primarily on symptoms of heartburn and regurgitation)
- Prevalence of clinically significant GERD is about 6%
- Frequent (daily or greater) GERD symptoms has been shown to have a negative impact on quality of life (QOL) in a systemic review of 19 studies
  - Increase in time off work and a decrease in work productivity
  - Sleep disturbance and impact on physical functioning
  - Nocturnal GERD has been shown to have a greater impact on QOL than daytime symptoms

GERD: Epidemiology
- Age-related features
  - Symptom frequency does not change but intensity of symptoms may decrease after age 50
  - Aging increases the prevalence of erosive esophagitis
  - Prevalence of Barrett's esophagus increases after age 50
- Gender-related features
  - Men are more likely to have erosive esophagitis and Barrett's esophagus
  - Women are more likely to have non-erosive disease (NERD)
Obesity and GERD

- An association between body mass index (BMI), weight gain, and waist circumference AND the presence of GERD symptoms and complications of GERD such as erosive esophagitis and Barrett’s esophagus has been demonstrated in several meta-analyses.
- There is a well-documented association between BMI and esophageal and proximal gastric adenocarcinoma.

GERD: Symptoms

- Typical symptoms
  - Heartburn, acid regurgitation, waterbrash
- Atypical symptoms
  - Non-cardiac chest pain, dyspepsia, epigastric pain, nausea, bloating and belching
- Alarm symptoms
  - Dysphagia, weight loss, GI bleeding, vomiting, anemia
- Extraesophageal symptoms
  - Chronic cough, hoarseness, laryngitis, and other airway symptoms.

GERD: Diagnosis

- Symptom presentation
- Response to anti-secretory therapy
- Radiographic studies
- Objective testing with endoscopy, esophageal manometry, and ambulatory pH monitoring
- *H. pylori* and GERD
Diagnosis: Symptoms and PPI Trial

- Presumptive diagnosis can be made on the basis of symptoms of heartburn and acid regurgitation
  - Systematic review of studies found the sensitivity of these symptoms for the presence of erosive esophagitis to be 30-76% with a specificity of 62-96%
- Empiric trial of PPI
  - A PPI trial is reasonable approach to confirm GERD when typical symptoms are present
  - Data from meta-analyses demonstrate a sensitivity of 78% and a specificity of 54%
  - The limitation of this approach is that a negative trial does not exclude GERD

Diagnosis: Barium radiographs

- Barium radiographs should not be used to diagnose GERD
- Barium radiographs with double contrast may detect signs of esophagitis but overall sensitivity is low
- Reflux above the thoracic inlet with or without provocation does increase the sensitivity but not enough to recognize as a diagnostic test for GERD

Diagnosis: Barium radiographs

- Barium radiographs are useful in patients with GERD in the following situations:
  - Dysphagia
  - Suspected contributing motility disorder
  - Evaluation for possible paraesophageal hernia or impalpable gastric volvulus
  - Pre-operative evaluation for fundoplication
**Diagnosis: Esophageal manometry**

- Limited value in the diagnosis of GERD
- Decreased lower esophageal sphincter pressures or the presence of a motility disorder are non-specific in nature
- Recommended to be used primarily before consideration of ant-reflux surgery to exclude achalasia or severe hypomotility such as is seen with scleroderma esophagus

**Diagnosis: pH monitoring**

- Ambulatory pH monitoring allows to determine the presence of abnormal esophageal acid exposure, reflux frequency, and symptom correlation
- Can be performed with telemetry capsule or transnasal catheter with or without impedance

**Diagnosis: pH monitoring**

- pH monitoring has excellent sensitivity (77-100%) and specificity (85-100%) in patients with erosive esophagitis but less so in those with endoscopy-negative symptoms
- Impedance added to pH monitoring may increase the sensitivity and be useful in those with non-acidic reflux
- Symptom correlation may be assessed using two association measures including symptom index and symptom association probability
- May be performed on or off therapy
- Indications: pre-operatively for patients with NERD, refractory GERD patients, and when the diagnosis is in question
Diagnosis: Upper endoscopy

- Primary tool used to evaluate the esophageal mucosa in patients with symptoms of GERD
- Findings of GERD may include erosive esophagitis, stricture, and a columnar lined epithelium confirmed to be Barrett's
- Endoscopy allows for biopsies of rings or strictures and for screening of Barrett’s esophagus
- Majority of patients with heartburn and regurgitation will have a negative exam (NERD)
When is endoscopy indicated in patients with suspected GERD?

- Presence of alarm symptoms or atypical symptoms
- Patients unresponsive to treatment
- Patients with non-cardiac chest pain
- Screening of high-risk patients
  - Epidemiologic risk factors for Barrett’s are male sex, age over 50, symptoms for > 5 years, and obesity
- Repeat endoscopy is not necessary in patients without Barrett’s unless new symptoms arise

Role of esophageal biopsies in GERD

- The sensitivity of histologic findings for GERD is of limited clinical usefulness
- Useful to exclude Barrett’s and to exclude non-GERD causes of symptoms such as eosinophilic esophagitis
- The use of routine biopsies of the esophagus in patients with heartburn and a normal endoscopy is not recommended to diagnose GERD

GERD and H. pylori

- Relationship between H. pylori infection and GERD is controversial
- Screening for H. pylori in patients with GERD is not indicated
- Treatment of H. pylori is not required as part of antireflux treatment
GERD and *H. pylori*

- Two potential concerns:
  - Does treatment of *H. pylori* exacerbate GERD symptoms? A large meta-analysis found no increase in GERD in patients with dyspeptic patients whether infection was eradicated or not.
  - Do patients on long-term PPI’s require screening for *H. pylori* to prevent the possibility of atrophic gastritis and cancer? Large FDA review concluded that the evidence was not sufficient to recommended testing of all patients on long-term PPI.

GERD: Management

- Lifestyle modifications
- Medical management
- Surgical options
- Refractory GERD
- Extra-esophageal symptoms

Lifestyle modifications

- Weight loss is recommended in patients who are overweight or have had recent weight gain
  - Multiple cohort and case-control studies have demonstrated reduction in GERD symptoms with weight loss and gastric bypass but not vertical banded gastroplasty
  - Head of bed elevation should be recommended in patients with nocturnal GERD
    - Three randomized controlled studies have shown decrease in symptoms and esophageal pH values with this intervention
- Routine elimination of foods that can trigger reflux is not recommended for GERD patients (low level of evidence)
  - Selective elimination could be considered if symptom correlation is present
Medical management

- Antacids
- Prokinetic agents (limited value in GERD in the absence of gastroparesis)
- Sucralfate (no role in the non-pregnant GERD patient)
- H2RA
- PPI's

H2-receptor antagonists

- H2RA's decrease the secretion of acid by inhibiting the histamine 2 receptor on the gastric parietal cell
- Limited efficacy in patients with erosive esophagitis
- H2RA's can be as a maintenance option in patients without erosive disease if symptom relief is achieved
- Bedtime H2RA therapy can be added to daytime PPI therapy in selected patients with nocturnal reflux
- Tachyphlaxis may limit effectiveness as a maintenance therapy

PPI's: General Overview

- PPIs are the most potent inhibitors of gastric acid secretion by irreversibly binding to and inhibiting the hydrogen-potassium ATPase pump
- PPIs should be used in patients who fail H2RA therapy and in patients with erosive esophagitis and/or frequent or severe GERD symptoms
- PPIs in standard doses for 8 weeks relieve symptoms and heal esophagitis in up to 86% of patients
- No major differences in efficacy among PPIs
PPIs: Indications and usage

- Traditional delayed release PPIs should be given 30-60 min before meal for maximal pH control.
- PPI therapy may be given in a step-up or step-down approach depending on severity of symptoms and degree of erosive esophagitis.
- Maintenance therapy should be given for GERD patients who continue to have symptoms after PPI is discontinued and in patients with erosive esophagitis and Barrett’s esophagus.
- Non-responders should be referred for evaluation.

PPIs: Concerns

- Switching PPIs can be considered in the setting of side effects.
- Patients with known osteoporosis can remain on PPI therapy.
- Concerns for hip fractures and osteoporosis should not affect the long-term use of PPI unless other risk factors present.
- PPI use can be a risk factor for *Clostridium difficile* infection.
- Short-term PPI (but not long-term) usage may increase the risk of community-acquired pneumonia.
- PPI therapy does not need to be altered with clopidogrel use as clinical data does not support an increased risk for adverse cardiovascular events.

Surgery for GERD

- Surgery is an option for long-term therapy in GERD.
- Surgical options include laparoscopic fundoplication or bariatric surgery in the obese.
- Reasons to consider surgery for GERD include: desire to discontinue medication, non-compliance, side effects, large hiatal hernia, refractory GERD.
- Pre-operative ambulatory pH monitoring and manometry is required in all patients considering anti-reflux surgery.
Surgery for GERD

- Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD
- Outcomes are significantly better when performed by a highly experienced surgeon
- Surgical therapy not recommended in patients who do not respond to PPI
- No effect on progression of Barrett’s esophagus
- Symptoms such as nausea, vomiting, and epigastric typically do not respond
- Up to 65% of patients back on medication at 10 years
- Long-term complications may include gas-bloat syndrome and dysphagia

Refractory GERD

- No established consensus regarding definition
- Patient-driven phenomenon
- First step is optimization of PPI therapy
- Exclude non-GERD etiologies (usually with upper endoscopy)
- Patients with refractory GERD and negative endoscopic evaluation should undergo ambulatory pH monitoring
- Reflux monitoring off medication can be done with any modality, testing on medication should include impedance
- Patients with negative testing are unlikely to have GERD and PPI should be discontinued

Extraesophageal symptoms of GERD

- GERD can be considered a co-factor in patients with asthma, chronic cough, or laryngitis
- An association between laryngeal and pulmonary symptoms and GERD has been shown but causality has not
- Careful evaluation for non-GERD causes is critical
- Diagnosis should not be made solely on the basis of laryngoscopy findings, especially edema and erythema
- Signs of laryngeal irritation was seen in >80% of healthy controls in a large prospective study
- Studies of ENT physicians blindly evaluating video recordings of laryngoscopic findings have shown poor concordance and intra-rater reliability was extremely valuable
Extraesophageal symptoms of GERD

- Extraesophageal symptoms occurring in isolation without concomitant symptoms of reflux are rare
- PPI trial is recommended in patients who also have typical symptoms of GERD
- No evidence to support empirical treatment in patients without typical reflux symptoms or objective evidence of GERD
- Upper endoscopy is not recommended as a means to establish a diagnosis of GERD in these patients
- Reflux monitoring should be considered before a trial of PPI in those patients without typical symptoms of GERD

GERD complications

- Erosive esophagitis
- Peptic strictures
- Schatzki ring
- Barrett’s esophagus

Barrett’s Esophagus: Definition

Barrett’s esophagus is the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer replaces the stratified squamous epithelium that normally lines the distal esophagus.
Barrett’s Esophagus: Impact on the patient

- Annual incidence of esophageal cancer in patients with Barrett’s is 0.5% per year (1 in 200 patients develop esophageal cancer)
- However, on an actuarial basis the impact on overall life expectancy is low
- Mortality from cardiovascular disease may be increased in patients with Barrett’s perhaps because both are associated with obesity
- Patients with Barrett’s report a lower QOL

Barrett’s Esophagus

- The management of patients with Barrett’s involves three major components:
  - Treatment of the associated GERD
  - Endoscopic surveillance to detect dysplasia
  - Treatment of dysplasia

Barrett’s Esophagus: Treatment of GERD

- Management principles are similar to GERD patients without Barrett’s
- The efficacy of PPI therapy solely for cancer prevention in Barrett’s esophagus has not been established in long-term clinical trials
- The risks and benefits of long-term PPI therapy in patients should be discussed in the context of their overall health status
- Generally, most recommend long-term PPI therapy
- Anti-reflux surgery is not more effective than medical therapy for the prevention of cancer in Barrett’s esophagus
Barrett’s Esophagus: Screening

- Screening for Barrett’s esophagus is not routinely recommended in patients with GERD.
- Patients at high risk for GERD-related complications should be considered for upper endoscopy (males, age over 50, white race, chronic GERD symptoms for >5 years, and presence of obesity).

Barrett’s Esophagus: Endoscopic Surveillance

- Endoscopic surveillance is performed primarily to detect dysplasia.
- Recommendations regarding surveillance are based upon assumptions that Barrett’s esophagus adversely affects survival and that surveillance can reduce mortality.
- Survival benefit has not been demonstrated in randomized prospective trials.
- Based on observational data, endoscopic surveillance is recommended in patients with Barrett’s esophagus.

Barrett’s Esophagus: Endoscopic Surveillance

- Current guidelines for endoscopic surveillance:
  - No dysplasia: 3-5 years
  - Low-grade dysplasia: 6-12 months
  - High grade dysplasia in the absence of eradication therapy: 3 months
  - Indefinite for dysplasia: 6 months.
Barrett’s Esophagus: Dysplasia

Low-grade dysplasia

High grade dysplasia

Barrett’s Esophagus: Treatment of Dysplasia

• If dysplasia is noted, it should be verified by a second pathologist with expertise in esophageal histopathology

• Treatment of high-grade dysplasia:
  – Esophagectomy
  – Endoscopic therapies that ablate the neoplastic tissue
  – Endoscopic mucosal resection

• Treatment of low-grade dysplasia:
  – Intensive surveillance with biopsies every 6 months
  – Endoscopic therapies that ablate the neoplastic tissue

Barrett’s Esophagus with Dysplasia

Esophagectomy

• Most patients with high-grade dysplasia (70-80%) can be treated successfully with endoscopic ablative therapies

• Esophagectomy is an alternative but is associated with a higher mortality and morbidity than ablative techniques

• Before proceeding to esophagectomy for high-grade dysplasia or intramucosal carcinoma, referral to a center specialized in management of foregut cancers and high-grade dysplasia
Barrett’s Esophagus with Dysplasia: Endoscopic Therapy

- The goal of endoscopic ablative therapies use thermal, photochemical, or radiofrequency energy to ablate the abnormal epithelium in Barrett’s esophagus.
- The second goal of endoscopic eradication therapy is to achieve reversion to normal-appearing squamous epithelium within the entire length of esophagus (data show that this can persist for up to 5 years).
- The most commonly used treatments include radiofrequency ablation (RFA) and photodynamic therapy.
- Endoscopic mucosal resection (EMR) can be used in combination with ablative therapies.
- RFA is most common ablative therapy utilized and is associated with less complications and “buried” metaplastic tissue than other techniques.

Barrett’s Esophagus: Dysplasia with nodule

- Patients with a visible dysplastic nodule may be candidates for endoscopic resection.
- Endoscopic mucosal resection (EMR) involves excision of a large segment of mucosa down to the submucosa.
- EMR can be utilized alone or in combination with ablative therapies.
- EMR is recommended in patients who have dysplasia in Barrett’s esophagus associated with a visible mucosal irregularity to determine the T stage.

Barrett’s Esophagus: Endoscopic Mucosal Resection

- Patients with dysplasia in Barrett’s esophagus may be candidates for EMR.
- EMR involves excision of a large segment of mucosa down to the submucosa.
Barrett’s Esophagus with Dysplasia: Radiofrequency Ablation

- Radiofrequency ablation (RFA) uses radiofrequency energy delivered by a balloon or that has a series of closely spaced electrodes.
- RFA rapidly generates a circumferential thermal injury with controlled depth and uniformity.
- Low rates of stricture formation and buried metaplasia are seen; other potential complications include chest pain and GI bleeding.
- Usually requires a follow-up circumferential ablation 12 weeks after the initial treatment.

Radiofrequency Ablation

- Ablation catheters are mounted on an articulated platform to ensure optimal tissue contact.
- Newer catheters can be passed through the scope.
- Used in conjunction with the balloon to treat focal areas of Barrett’s epithelium.
Barrett’s Esophagus with Low-grade Dysplasia: Endoscopic Therapy

- Risk of cancer in these patients is poorly defined
- Intensive surveillance is an option
- RFA therapy in patients with low grade dysplasia is highly effective and can lead to reversion to normal-appearing squamous epithelium in >90% of cases

Barrett’s Esophagus with High-grade Dysplasia: Endoscopic Therapy

- Rate of cancer development is 4-8 percent per year in patients with high grade dysplasia
- RFA therapy for patients with high grade dysplasia reduces progression to esophageal cancer in a randomized controlled trial
- Several uncontrolled trials have shown similar reduction in cancer development and sustained reversion of squamous epithelium in a large portion of patients
- EMR can be utilized with RFA for visible mucosal lesions

Conclusions

- GERD can usually be diagnosed on the presence of heartburn and regurgitation
- Empiric trial of PPI may be useful in confirming the diagnosis of GERD in patients with typical symptoms
- Alarm symptoms and atypical symptoms require additional evaluation, usually with upper endoscopy
- PPIs are effective and can be used safely in most, with osteoporosis and concomitant clopidrogel
- GERD may be a co-factor in certain laryngeal and pulmonary diseases and a PPI trial can be considered in those patients with typical GERD symptoms
- Refractory GERD may require additional testing including ambulatory pH monitoring
Conclusions

- Endoscopy should be considered in patients at high risk for erosive esophagitis and Barrett’s esophagus (white race, male sex, age > 50, chronic GERD >5 years, and obesity)
- Endoscopic surveillance is recommended for patients with Barrett’s esophagus
- A diagnosis of dysplasia should be independently confirmed by a second pathologist with esophageal expertise
- High grade and low grade can be treated effectively with endoscopic techniques such as EMR and RFA alone or in combination with associated prolonged reversion to squamous epithelium