Barrett's Esophagus: How GERD can Lead to Esophageal Cancer

Scott Hendrickson, DO, FACOI
Gastroenterologist
Cancer Treatment Centers of America
Oklahoma Osteopathic Association
April 30, 2015

Objectives

• GERD/Erosive esophagitis
  – Review:
    • Pathophysiology
    • Diagnosis
    • Treatment
    • Link to Barrett’s esophagus

• Barrett’s esophagus
  – Review:
    • Pathophysiology
    • Diagnosis/screening
    • Treatment

GERD

• Facts
  – Gastroesophageal reflux is physiologic
  – GERD is consequence of gastric contents moving retrograde effortlessly from stomach to esophagus
  – 44% of Americans experience heartburn or acid regurgitation at least once/month
  – Only 7% of patients have erosive esophagitis
  – Caucasian males have higher incidence of esophagitis than African Americans, Asians
  – Prevalence in most Asian countries much lower- low fat diet, lower BMI, H. pylori effect?
GERD

- Mechanisms for reflux
  - Transient lower esophageal sphincter relaxations
  - Hypotensive LES-uncommon
  - Hiatal hernia
    - Commonly associated
    - Direct correlation controversial
  - Reduced esophageal acid clearance
    - Decreased salivation
      - Cigarette smoking, Xerostomia
      - Water brash is copius salivation (esophagosalivary reflex)
  - Tissue resistance
    - Microscopic changes in the mucosa

- Symptoms
  - Frequency and severity of heartburn does not predict degree of damage
  - Up to one third of patients with Barrett’s do not have symptoms
  - Dysphagia
  - “Water brash”
  - Chest pain
  - Reflux-induced asthma
  - Reflux laryngitis
  - Chronic cough
  - Dental erosion
GERD

- Diagnosis
  - Empiric trial of acid suppression
    - Omeprazole 40mg BID for 2 weeks
  - Endoscopy
    - Major role is to diagnose and treat GERD complications and to define Barrett’s esophagus
    - Only 20% to 60% sensitivity
    - Alarm symptoms should initiate endoscopy
      - Dysphagia, odynophagia, wt. loss, bleeding
    - Los Angeles Classification
    - Esophageal pH monitoring/impedance
      - Before fundoplication, symptomatic pts with normal endoscopy, extraesophageal manifestations

Ph/Impedance Monitoring

- Catheter-free pH Monitoring System
  - Radiotransmitter placed in esophagus with data recorder worn by patient; capsule passes through the digestive tract.
- Combined impedance and pH monitoring
  - Allows measurement of acid and nonacid reflux
  - Reasonable choice for monitoring
  - Values and interpretation of nonacid reflux not as well characterized and difficult to interpret

Treatment

Prescription / Over the Counter Medicine

*$300 / Meds*
GERD

• Treatment
  – Prognosis depends greatly on whether they have erosive or non-erosive disease, pts unlikely to cross over to other group
  – Lifestyle modifications
    • Proven in studies: elevation of head of bed, left lateral decubitus position, and weight loss
  – OTC meds-usually for infrequent heartburn episodes, do not heal esophagitis
    – Antacids, Gaviscon, H2RAs
  – PPIs-much more effective in healing esophagitis, especially LA grade C/D

Food and Medications that may Worsen GERD Symptoms

<table>
<thead>
<tr>
<th>Foods</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic beverages</td>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Carbonated beverages</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Citrus fruit drinks</td>
<td>Caffeine</td>
</tr>
<tr>
<td>Chocolate</td>
<td>Calcium channel blockers (e.g. dihydropyridine)</td>
</tr>
<tr>
<td>Coffee</td>
<td>Nicotine</td>
</tr>
<tr>
<td>Fatty Foods</td>
<td>Nitrates</td>
</tr>
<tr>
<td>Peppermint</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Spicy foods</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Tomato products</td>
<td></td>
</tr>
</tbody>
</table>

GERD

• Treatment
  – Surgery
    • Fundoplication
      – Candidates:
        « Pts controlled on PPI desiring alternative treatment
        « Pt with volume regurgitation, aspiration, uncontrolled on PPIs
        « Recurrent peptic strictures in young pts
        – Extensive testing must be done pre-op to rule out other conditions (gastroparesis, achalasia, Barrett’s, etc)
        – Barrett’s esophagus does not regress
        – Post-op dysphagia – 19%
        – 25%-60% are back on acid-suppressive med in 5-15yrs
        – High-volume centers have better outcomes
Fundoplication

GERD

• Treatment
  – Endoscopic
    • Stretta, Enteryx, Gatekeeper, EndoCinch - none have proven safety, efficacy at this time

Barrett’s Esophagus Epidemiology

• Barrett’s esophagus is the condition in which metaplastic columnar epithelium replaces squamous epithelium in the distal esophagus
• Develops as a consequence of GERD
• Predisposes to the development of adenocarcinoma
• Usually discovered in middle-aged individuals undergoing endoscopy, mean age of 55
• Acquired condition, not congenital
• Uncommon in African Americans, Asians
• Male to female ratio 2:1
• Prevalence varies from 0.9 to 20 percent (depending on population studied)
Epidemiology

- Prevalence 5.6% in patients with no history of heartburn
- Prevalence 10-15% in patients with chronic GERD
- Sensitivity of endoscopy for detection approximately 80%
- Prevalence may be higher in patients with peptic strictures

Diagnostic Criteria

- Two criteria must be fulfilled:
  - Documentation of columnar epithelium in the distal esophagus
  - Histologic examination must reveal specialized intestinal metaplasia (gastric cardia-type epithelium not definitive)

Diagnostic Criteria, Continued

- Squamocolumnar (Z-line) and gastroesophageal (GEJ) junctions must be identified to further classify Barrett’s esophagus
  - Long segment Barrett’s-distance between Z-line and GEJ >3cm
    - Pts tend to have more severe reflux (upright and supine)
  - Short segment Barrett’s-distance between Z-line and GEJ <3cm
    - Less severe reflux (upright), higher LES pressures
- Identification of cardia-type epithelium above the Z-line is likely a precursor to intestinal metaplasia
Barrett's Esophagus

Pathophysiology

- Barrett's esophagus develops through the process of metaplasia
  - Tissue chronically exposed to noxious factors (reflux) promoting repair and aberrant differentiation
  - Metaplastic columnar cells appear to be more resistant to reflux-induced injury
  - Pattern of reflux may predispose to neoplasia
    - Pulsed acid exposure increases cell proliferation
    - Continuous acid exposure decreases proliferation

Barrett's Esophagus

- Metaplasia-dysplasia-carcinoma sequence
Dysplasia and Adenocarcinoma

- Estimates of cancer risk with Barrett's
  - General population - 0.5% per year
  - High-grade dysplasia - 5-8% per year
  - Low-grade dysplasia - poorly defined, somewhere between general population and high-grade

Screening

- There is no convincing evidence to suggest routine screening (endoscopy) of patients with GERD
- 40% of patients with adenocarcinoma of the esophagus had no history of GERD
- Studies have failed to prove targeted screening of patients with GERD has prevented deaths from adenocarcinoma
- Symptoms suggesting complicated GERD should undergo endoscopic evaluation:
  - Anorexia, wt loss, dysphagia, bleeding, odynophagia
- Patients with chronic GERD are more likely to have Barrett's and therefore more likely to benefit from endoscopy

Barrett's Esophagus

- Management
Management

• Three major components:
  – Treatment of the associated GERD
  – Endoscopic surveillance to detect dysplasia
  – Treatment of dysplasia
• Treatment of GERD
  – Similar principles to patients without Barrett’s
  – Anti-reflux surgery
    • Does not appear to be more effective than medical therapy for preventing adenocarcinoma

Management

• Treatment of GERD
  – Control of gastric secretion may be difficult to due profound reflux diathesis (not resistance to PPIs)
  – May consider addition of nocturnal H2RA
  – Proliferation and differentiation markers improve in bx specimens when GERD is well controlled (suggesting prevention of carcinogenesis)
  – Timing of acid suppression may be important in the influence on progression to cancer (starting therapy early in the disease process)

Management Guidelines

• American College of Gastroenterology
  – Screening remains controversial, highest yield is in >50 Caucasian males with longstanding heartburn
  – The grade of dysplasia determines surveillance interval (should confirm by expert pathologist)
  – Low-grade dysplasia- repeat endoscopy in 6 months, if no high-grade dysplasia found then yearly until two consecutive exams without dysplasia
  – High-grade dysplasia (flat mucosa)- repeat endoscopy in 3 months, irregular mucosa should undergo endoscopic mucosal resection for staging
  – High-grade dysplasia pts should be counseled regarding therapeutic options (intensive surveillance, esophagectomy, ablation)
Management

- **Endoscopic surveillance**
  - Survival benefit has not been demonstrated in randomized prospective studies
  - Surveillance is complicated by many variables involved in deciding the benefit
    - Variable incidence of dysplasia/carcinoma
    - Risk of the procedure
    - Quality of life after invasive procedures

- **Evidence supporting surveillance**
  - Observational studies have shown a benefit in detecting curable dysplasia and asymptomatic cancers are less advanced
  - Surveillance is performed primarily to detect dysplasia, which is the precursor to cancer
    - However, the rate of progression from dysplasia to cancer is unclear
    - Low-grade dysplasia is not diagnosed reliably (significant discrepancy between studies, criteria)

- **Detecting dysplasia**
  - Often patchy and can be easily missed
  - Extensive random biopsies can help reduce sampling error
  - Several endoscopic techniques can help detect subtle mucosal changes
    - Chromoendoscopy, confocal microendoscopy, narrow band imaging, autofluorescence, high-resolution white light endoscopy
Barrett’s Esophagus: Narrow-Band Imaging

Management

- Treatment of high-grade dysplasia
  - Esophagectomy
  - Endoscopic ablation therapies
  - Endoscopic mucosal resection
  - Intensive endoscopic surveillance until bx reveals adenocarcinoma
Management

• Esophagectomy
  – Only definitive therapy to remove all neoplastic epithelium
  – Highest rate of procedure-related mortality and long-term morbidity (mortality 3-12%)
  – Minimally invasive techniques are being developed (currently similar morbidity/mortality but shorter hospital stays)
  – Mortality probably less than 5% in healthy patients with early neoplasia

Esophagectomy

Management

• Endoscopic ablative therapies
  – Radiofrequency ablation (HALO system)
    • Ablates Barrett’s using radiofrequency energy delivered by a balloon with series of closely spaced electrodes
    • Rapidly generates a circumferential thermal injury with controlled depth and uniformity
    • May have lower rates of stricture formation and buried metaplasia
    • Trials have shown 90.5% eradication with low-grade dysplasia, 81% with high-grade dysplasia
Management

• Photodynamic therapy
  – (PDT) is based upon the ability of chemical agents, known as photosensitizers, to produce cytotoxicity in the presence of oxygen after stimulation by light of an appropriate wavelength
  – After systemic injection, the photosensitizer is absorbed by most tissues, but for reasons not yet clearly understood, it is selectively retained at a higher concentration by neoplastic tissue
  – Effective for eradication of dysplastic BE but higher rate of complications (stricture, esophagitis, ulceration)
  – Photosensitizer can remain in skin for up to 30 days

Photodynamic Therapy
Management

• Cryotherapy
  – Cryotherapy system is used to apply cold nitrogen or carbon dioxide gas endoscopically to the Barrett's esophagus
  – Indicated for dysplastic BE
  – Observational studies suggest it will eradicate high-grade dysplasia in approximately 95 to 100 percent of patients
  – Low rate of complications
**Endoscopic Resection**

- Excision of a large segment of esophageal mucosa down to the submucosa
- Provides large-tissue specimens that can be examined by the pathologist to determine the character and extent of the lesion, and the adequacy of resection
- Can also be combined with endoscopic ablative therapies for the eradication of Barrett's mucosa in patients who have visible lesions
- Guidelines recommend ER for the treatment and staging of nodular BE and suspected intramucosal adenocarcinoma

**Endoscopic Mucosal Resection**

**Chemoprevention**

- Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit cyclooxygenase (COX), may protect against the development of Barrett's esophagus or progression of BE
- Inhibition of COX-2 has been shown to have anti-proliferative and pro-apoptotic effects in Barrett's-associated esophageal adenocarcinoma cell lines
- Unclear if benefit outweighs adverse GI side effects
- Large trial in UK ongoing
Summary

• GERD is a very common problem in the U.S. that can eventually progress to Barrett’s esophagus and eventually esophageal adenocarcinoma
• Screening of at-risk individuals and surveillance of BE may lead to a reduction in the incidence of this aggressive form of cancer
• Effective treatments are available for eradication of BE

Questions?