Barrett’s Esophagus
Definition of GERD –
American College of Gastroenterology

“GERD is defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus”
Definition of GERD – Genval Workshop

“The term GERD should be used to include all individuals who are exposed to the risk of physical complications from gastro-esophageal reflux, or who experience clinically significant impairment of health-related well-being (quality of life) due to reflux-related symptoms, after adequate reassurance of the benign nature of their symptoms”
GERD – two main categories

GERD with erosive esophagitis

GERD without erosive esophagitis
Erosive Esophagitis
Symptoms are not reliably predictive of mucosal damage

Patients with and without erosive esophagitis are similar with respect to symptom severity\(^1\)

Patients with and without erosive esophagitis are similar with respect to symptom frequency\(^1\)

Patients with different grades of erosive esophagitis are similar with respect to symptom severity\(^2\)

\(^1\)Smout. Aliment Pharmacol Ther 1997
\(^2\)Lundell et al. Gut 1999
Symptoms associated with GERD

Heartburn

Typical symptoms other than heartburn

Atypical symptoms
Other typical symptoms of GERD

Regurgitation

Dysphagia
**Atypical symptoms of GERD**

<table>
<thead>
<tr>
<th>Throat clearing</th>
<th>Chest pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Globus</td>
<td>Hoarseness</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>Chronic cough</td>
</tr>
<tr>
<td>Dental erosion</td>
<td>Sore throat</td>
</tr>
<tr>
<td></td>
<td>Wheezing</td>
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</table>
Pathogenesis of GERD – overview

GERD results from exposure of the esophageal mucosa to refluxed gastric contents

In most patients with GERD, exposure of the esophagus to refluxate is greater than normal

In a minority of patients, exposure is within normal limits; in these patients, GERD may be due to decreased mucosal resistance to refluxate
Causes of increased exposure of the esophagus to gastric refluxate

- Defective esophageal clearance
- Lower esophageal sphincter (LES) 'dysfunction'
- Hiatal hernia
- Delayed gastric emptying
- Increased intra-abdominal pressure
Complications of GERD

Esophageal
- Barrett’s esophagus
- adenocarcinoma
- stricture
- ulceration
- bleeding

Extra-esophageal
- asthma
- reflux laryngitis
- vocal cord ulcers
- subglottic stenosis
- tracheal stenosis
Barrett’s definition

Any presence of metaplastic columnar epithelium that replaces the normal stratified squamous epithelium in the esophagus

Biopsy has to show intestinal metaplasia

Develops as a consequence of GERD

Predisposition to development of Adenocarcinoma of the esophagus
Barrett’s Esophagus clinical significance

Premalignant lesion for esophageal adenocarcinoma

Patients with Barrett’s esophagus may be 30–60 times more likely to develop this cancer than the general population

The reported incidence of Barrett’s esophagus is rising
Barrett’s Esophagus: premalignant lesion

Normal

Endoscopy-negative reflux disease

Erosive esophagitis

?  

Barrett’s esophagus (5-20%)

?  

Dysplasia

Esophageal adenocarcinoma
Occurs in 0.9-20% population

- Long segment (> 3 cm) 3-5%
- Short segment (< 3 cm) 10-15%

Male: Female ratio 2:1

- Progression to HGD/Carcinoma (2x)

Uncommon in African Americans and Asians

Average age of diagnosis is 55 y/o

## Prevalence of Barrett’s Esophagus in General Population of Sweden

<table>
<thead>
<tr>
<th></th>
<th>BE</th>
<th>LSBE (≥ 2cm)</th>
<th>SSBE (&lt; 2cm)</th>
<th>No BE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases (%)</strong></td>
<td>16 (1.6%)</td>
<td>5 (0.5%)</td>
<td>11 (1.1%)</td>
<td>984 (98.4%)</td>
</tr>
<tr>
<td><strong>% with GERD symptoms</strong></td>
<td>56.3%</td>
<td>80.0%</td>
<td>45.5%</td>
<td>39.7%</td>
</tr>
<tr>
<td><strong>% with esophagitis</strong></td>
<td>25.0%</td>
<td>60.0%</td>
<td>9.1%</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

Extent of Barrett’s

(889 patients underwent EGD)

Long Segment (> 3 cm): 1.6%

Short Segment (< 3 cm): 6.4%

GEJ Barrett’s (at Z-line): 5.6%

Long Segment Barrett’s vs Short

Longer history GERD
Worse 24 hour pH studies
  • Increased proximal esophageal acid exposure
More upright and supine GERD
Lower LES pressure measurements
Decreased esophageal peristalsis amplitude
Higher prevalence of Dysplasia (24% vs. 8%)
Higher likelihood to have carcinoma

Risk of cancer in Barrett’s

Variable incidence rates in various studies
0.5% /year accepted with no dysplasia precursor

HGD → Cancer (5-8%/yr)
LGD → Cancer (??)

Increases with age
Increased with weekly GERD
Increased in males

Screening for Barrett’s Esophagus

Meta analysis:

• 1189 patients with cancer & 4666 controls

• Patients with weekly GERD symptoms were more likely to have cancer (odds ratio 4.9)

• Patients with daily GERD symptoms were more likely to have cancer (odds ratio 7.4)

• Patients with no symptoms or less than weekly GERD were not as likely

• > 40% patients had no GERD symptoms

Rubenstein, et al, Alim Pharm Ther; 2010;32:1222
Screening for Barrett’s Esophagus: Problems

Relatively few cases of esophageal adenocarcinoma

- 5% esophageal cancers occur in known Barrett’s

High prevalence of GERD

*No prior GERD symptoms* in 40% of adenocarcinoma patients

EGD & pathology diagnostic inconsistencies

No clear evidence that has impact on mortality
AGA Recommendation for Screening

>50 y/o
Males
White
Chronic GERD at least weekly
Hiatal hernia
Increased BMI
Intra-abdominal body fat distribution

Gastroenterology 2011; 140: 1084
Surveillance of Barrett’s
Barrett’s Esophagus: The Prague Classification

Good interobserver reliability

Barrett’s Esophagus: Technique of Endoscopic Surveillance

1. Define Landmarks

2. 4 quadrant biopsies q 2 cm

Endoscopic Surveillance (limitations?)

Observational studies
• Detect curable dysplasia and cancer at earlier stage

Dysplasia/early cancer
• Indistinguishable
• Patchy distribution

Interobserver variability in dysplasia interpretation

*Most patients never develop cancer*
• Incidence 0.5%/year
Confocal Images

(Esophagus)
Barrett’s Treatment Modalities

**PPI acid suppression**
- Symptoms of acid reflux or esophagitis on endoscopy
- Reduction of HGD dysplasia or cancer progression (indirect evidence)
- pH studies show pathological acid reflux in patients with Barrett’s on PPI therapy

**Aspirin/NSAIDs/Statins**
- 2009 meta-analysis suggest ASA/NSAID associated with less cancer
- Celecoxib not shown to reduce progression to dysplasia/cancer
- COX-2 inhibitors may carry high cardiac risk
- Meta-analysis with statin showed 28% reduction in cancer risk/Barrett’s

**Surgical Fundoplication**
- Not more effective than medical therapy to prevent cancer
- Show similar partial regression of Barrett’s as in PPI
- Decrease rate of cancer (uncontrolled studies)
Barrett’s Treatment Modalities

Ablation Options:

- Endoscopic Mucosal Resection (EMR)
- Argon Plasma Coagulation (APC)
- Bipolar Coagulation
- Laser Coagulation
- Radiofrequency Ablation (RFA)
- Cryo-ablation
- Photodynamic therapy (PDT)
Treatment for Barrett’s (HGD)

Radiofrequency Ablation

Bipolar array
Electrical field
Frictional heating of water
Ablation of the mucosa
Randomized sham trial

- 127 patients
- At 1 year follow up
  - LGD 91% eradicated vs. 3%
  - HGD 81% eradicated vs. 19%
  - Fewer cancers 1% vs. 9%
Anatomy and RFA

Targeted Epithelium
Thickness ~500µm

RFA
Ablation depth 500-1,000µm

Approximate EMR Depth

Esophageal epithelium ~500µm
Lamina Propria
Muscularis Mucosae
Submucosa
Muscularis Propria
Circumferential Ablation (Radiofrequency ablation)
Immediate Ablation Effect (Radiofrequency ablation)
Ablation with HALO90
LN CryoSpray Ablation (CSA)
The freeze-thaw cycle

- Ice crystals disrupt lipids and cytoskeleton
- Ischemia and vascular stasis
- Reperfusion injury with cellular leakage and submucosal hemorrhage
- Inflammatory response
- Immune stimulation
LN Cryotherapy Depth of Injury

1 hour: minimal inflammation

48 hours: marked inflammation

Johnston Gastrointest Endosc 2001 A3448
LN Cryotherapy Advantages

High patient tolerance
- Minimal chest pain
- Familiarity with concept

Able to treat uneven surfaces

Possible to treat submucosal lesions
LN Cryotherapy Risks

Strictures 4%
• Appears limited to those with prior narrowing or therapy

Lip ulcer

Pain usually mild – 0 to 5 days
LN Cryotherapy and Squamous Cell Cancer

Invasive SCC
Treatment for HGD

Endoscopic
- EMR
  - Can remove early cancers and give staging information
  - Best results when used with ablative therapy
- PDT
  - Increased complications, buried glands
  - 15% eventually developed cancer
- APC
  - Buried glands, incomplete destruction

Surgical
- Esophagectomy
  - Removes all tissue absolutely
  - Mortality 3-12%, morbidity

Surveillance
- Biopsy every 3 months
- Increased cancer risk compared to ablative therapy
Treatment for LGD

Efficacy for cancer prevention not established

? How long ablation will last

Still need to perform EGD for surveillance

Too many unanswered questions
AGA Recommendations

Screen
• >50 y/o, male, white
• Chronic GERD, hiatal hernia
• Increased BMI, intra-abdominal fat distribution

Treat
• PPI if drug risk is low
• ASA?? (only if cardioprotective)

Surveillance
• No dysplasia: 3-5 years
• LGD: 6-12 months
• HGD: 3 months

Therapy
• HGD: eradication with RFA, PDT, EMR, Cryo
• HGD: young pts, long segment Barrett’s, multifocal