Acid Reflux in the 21st Century

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Florida Atlantic University
GERD is a common and significant problem: US study

Prevalence (%)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Any episode of GERD symptoms</th>
<th>At least weekly episodes of GERD symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>25–34</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>35–44</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>45–54</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>55–64</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>65–74</td>
<td>30</td>
<td>2</td>
</tr>
</tbody>
</table>

Locke GR et al. Gastroenterology 1997;112:1448.
GERD has a greater impact on quality of life than other common diseases.

- Psychiatric patients
- Esophagitis, untreated
- Duodenal ulcer, untreated
- Angina pectoris
- Heart failure (mild)
- Normal female
- Normal male
- Hypertension, untreated

PGWB Index score

Clinical Presentation of GERD

Typical/Esophageal
- Heartburn
- Acid regurgitation

Atypical/Supraesophageal
- Chest pain
- Laryngitis
- Asthma
- Sinusitis
- Chronic cough
- Aspiration pneumonia
- Tooth decay
Pathophysiology of GERD

Impaired acid neutralization by saliva and $\text{HCO}_3^-$

Impaired esophageal motility

LES (inappropriate relaxation)

Hiatal hernia

Delayed gastric emptying/gastroparesis

LES = lower esophageal sphincter
Medications may aggravate GERD symptoms

**Impairment of LES function:**
- beta-adrenergic agonists
- theophylline
- anticholinergics
- tricyclic antidepressants
- progesterone
- alpha-adrenergic antagonists
- diazepam
- calcium channel blockers.

**Damage to the esophageal mucosa:**
- acetylsalicylic acid and other NSAIDs
- tetracycline
- quinidine
- bisphosphates.
Phenotypic Classification of GERD

NERD* 60-70%
Erosive Esophagitis 20-30%
Barrett’s Esophagus 6-10%

*NERD: Non-Erosive Reflux Disease

Fass et al. Alim Pharm Ther 2005
Symptomatic NERD

- Heartburn
- Regurgitation
- Chest pain
- Impaired QOL
- Others (burning mouth/tongue)
- Atypical (“supraesophageal”) symptoms
  - These are the same symptoms as patients with erosive esophagitis and Barrett’s esophagus
  - *The severity of these symptoms CANNOT PREDICT the subtype of GERD into which a patient falls prior to endoscopic examination*
Severity of Heartburn in Patients With and Without Esophagitis

Patients without esophagitis

Patients with esophagitis

No difference in severity of heartburn with respect to symptom duration

Smout et al., APT 1997; 11(suppl. 2):81
Los Angeles Classification of Erosive Esophagitis

- **GRADE A**: Minimal erosions
- **GRADE B**: Superficial erosions
- **GRADE C**: Deep erosions
- **GRADE D**: Ulceration
Endoscopic Images

Normal Squamocolumnar junction

LA Grade A Esophagitis

LA Grade D Esophagitis
Benign Distal Esophageal Stricture in Patient with GERD
Esophageal stricture – endoscopic appearance
Metaplasia of the esophagus: Barrett’s esophagus

Definition: a change in the esophageal epithelium of any length that can be recognised at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus and excludes intestinal metaplasia of the cardia.
Barrett’s esophagus is associated with prolonged acid reflux

Number of episodes

Time (minutes)

Barrett’s esophagus n=51
severe esophagitis n=30
moderate esophagitis n=45
controls n=24

The prevalence of Barrett’s esophagus increases with the duration of reflux symptoms.

Does Barrett’s Esophagus Occur in the Absence of Heartburn?

- EGD done on 961 pts scheduled for colonoscopy; 556 never had heartburn
- Conclusions:
  - BE is relatively common in persons age >40 years with no prior endoscopy
  - LSBE is very uncommon in patients who have no history of heartburn

<table>
<thead>
<tr>
<th></th>
<th>HB (-) (n=556)</th>
<th>Overall (n=961)</th>
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<tbody>
<tr>
<td>Barrett’s</td>
<td>5.6%</td>
<td>6.8%</td>
</tr>
<tr>
<td>LSBE</td>
<td>0.36%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

Rex D et al. Gastro 2003
Good News

- Protects against chemical injury
- Symptoms improve
Barrett’s Esophagus
0.5%/patient/year cancer
0.9%/patient/year HGD

Colon Polyp
0.5%/patient/year cancer
7.5M colonoscopies/year
Evolution of Barrett's (The Bad News)

- Squamous esophagus
- Chronic inflammation
- Barrett's metaplasia
- Low-grade dysplasia
- High-grade dysplasia
- Adenocarcinoma

Injury: Acid & bile reflux

Genetics: Gender, race, other factors (cox-2)

Accumulate Genetic Changes
## Baseline Mutations

<table>
<thead>
<tr>
<th>Pt.</th>
<th>IHC Ki-67</th>
<th>IHC p53</th>
<th>CEP 1</th>
<th>CEP 9</th>
<th>p16</th>
<th>p53</th>
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<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td><strong>Gain</strong></td>
<td>N</td>
<td><strong>Loss</strong></td>
<td><strong>Loss</strong></td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>N</td>
<td><strong>Loss</strong></td>
<td><strong>Loss</strong></td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>-</td>
<td><strong>Gain</strong></td>
<td><strong>Gain</strong></td>
<td><strong>Loss</strong></td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td><strong>Gain</strong></td>
<td>N</td>
<td><strong>Loss</strong></td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>[ ]</td>
<td>N</td>
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<td>N</td>
<td><strong>Loss</strong></td>
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<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td><strong>Gain</strong></td>
<td>N</td>
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<td><strong>Loss</strong></td>
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<tr>
<td>7</td>
<td>+</td>
<td>+</td>
<td><strong>Gain</strong></td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td><strong>Gain</strong></td>
<td><strong>Gain</strong></td>
<td><strong>Loss</strong></td>
<td><strong>Loss</strong></td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td><strong>Loss</strong></td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td><strong>Loss</strong></td>
</tr>
</tbody>
</table>
Risk of Progression to EAC

- Male
- Caucasian
- Smoker
- Obese
- Family history
- Length of Barrett’s
- Size of hiatal hernia
- Duration of Barrett’s

Chak, Gut, 2002
Gopal, Dig Dis Sci, 2003
Weston, Am J Gastroenterol, 2004
Hage, Scand J Gastroenterol, 2004
Iftikhar, Gut, 1992
Bani-Hani, World J Gastroenterol, 2005
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Prasad, Am J Gastroenterol, 2010

Reid, Am J Gastroenterol, 2000
Weston, Am J Gastroenterol, 2001
Suspiro, Am J Gastroenterol, 2003
Sikkema, Am J Gastroenterol, 2011
Sappati Biyyani, Dis Esophagus, 2007
Munitiz, J Clin Gastroenterol, 2008
Abnet, Eur J Cancer, 2008
de Jonge, Am J Gastroenterol, 2006
Lagergren, Ann Intern Med, 1999
Jung, Am J Gastroenterol, 2011
Esophageal Cancer

From: Pohl H, Welch HG. Natl Cancer Inst 2005

Graph showing the rate ratio of various cancers over time from 1975 to 2000. The cancer types include Esophagus, Melanoma, Prostate, Lung/Breast, and Colorectal.
Esophageal Cancer: 5-Year Survival

Treatment

- GERD
- Barrett’s
- Esophageal adenocarcinoma
A 35-year old woman presents to her primary care physician because of six months of heartburn. Her medical history is only notable for chronic migraines. She has no dysphagia, odynophagia, or weight loss. She experiences symptoms several times a week, usually during stressful days at her job as a high school teacher.

• What should be done at this point?
Initial Management of GERD

Step-up vs Step-down
Initial Management of GERD

A. Antacids and lifestyle changes
B. $H_2$-receptor antagonists
C. Standard Proton pump inhibitor therapy
D. High-dose Proton pump inhibitor therapy
   - Continuous?
   - On-Demand?
E. Endoscopy and/or pH testing followed by therapy based on results
Changes to diet and lifestyle can impair quality of life without improving GERD symptoms

• Changes to diet and lifestyle are difficult for some patients and can significantly impair patient quality of life.

• Studies into the negative effects of diet and lifestyle on GERD are few in number and the findings are statistically weak.

• The criteria for evidence-based medicine are not met when diet and lifestyle changes are recommended.
Treatment Goals for GERD

- Eliminate symptoms
- Heal esophagitis
- Manage or prevent complications
- Maintain remission
Mechanisms of Action of GERD Pharmacotherapy

Antacids neutralize secreted HCl.
PPIs block acid at its source in the proton pump.

H$_2$RAs block the histamine receptor, interfering with one of the stimulation pathways.

ACh=acetylcholine
Proton Pump Inhibitor Test

- Empiric therapy with PPI for heartburn
- Functions as both diagnostic test and therapeutic trial
- Sensitivity 68-80% as defined by abnormal pH test or endoscopy
- May be falsely positive (does not actually make a true diagnosis or GERD)

Kahrilas PJ. Am J Gastro 2003;98: S15-23
PPI Complications

• Dementia: increased likelihood in observational study
• Chronic Kidney Disease
The PCP places her on H₂-receptor antagonists and recommends lifestyle changes and intermittent antacids. She returns a month later with no change in her symptoms. She is placed on once daily PPI therapy and 2 weeks later, she is still symptomatic.

*What should be done now?*
Indications for additional investigations

• Symptoms are frequent and long-standing or do not respond to therapy.
• Atypical history.
• Alarm symptoms are present:
  – severe dysphagia
  – weight loss
  – bleeding
  – hematemesis
  – mass in the upper abdomen
  – anemia
A. Refer for endoscopy
B. Increase proton pump inhibitor to BID
C. Perform pH study
D. Refer for surgical treatment
Why Do PPI’s Fail to Control Symptoms?
Reasons for PPI “Failure”

- Patient non-compliance
- Persistent esophageal acid exposure
  - Hypersecretory state
  - Large hiatal hernia
  - Nocturnal acid breakthrough
- Acid-sensitive esophagus
- Non-acid reflux
- Wrong diagnosis
- Functional heartburn (NOT GERD!!)
Placement of Bravo® capsule
Antireflux surgery – an alternative to pharmacological therapy

• The efficacy of antireflux surgery in controlling GERD is similar to that of chronic PPI therapy.
• The outcome of antireflux surgery is highly dependent on the skill and experience of the surgeon.
• Surgery does not always end the need for antisecretory therapy to control the symptoms of GERD.

Lundell et al 2001; Spechler et al 2001
Nissen fundoplication and the Toupet procedure

Nissen fundoplication

Toupet procedure
## Medication use in follow-up of patients from VA cooperative GERD study

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Medical Treatment Group (%)</th>
<th>Surgical Treatment Group (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any anti-reflux medication</td>
<td>92 (n = 90)</td>
<td>62 (n = 37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPIs</td>
<td>64 (n = 89)</td>
<td>32 (n = 37)</td>
<td>0.002</td>
</tr>
<tr>
<td>H₂RAs</td>
<td>65 (n = 88)</td>
<td>41 (n = 37)</td>
<td>0.02</td>
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<tr>
<td>Prokinetics</td>
<td>15 (n = 86)</td>
<td>8 (n = 36)</td>
<td>0.39</td>
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*Spechler et al, JAMA 2001; 285: 2331*
Barrett’s HGD Management Then: pre-2009

- Dysplasia and Early Cancer
Ablation Depth Control

Micro-array at Tissue Interface
Treatment options IM

- Radio frequency ablation (RFA)
- Cryotherapy
- Photodynamic therapy
- Endoscopic mucosal resection (EMR)
Radio Frequency Ablation

HALO^360+

HALO^90
Radio Frequency Ablation
RFA

Baseline  Post-RFA  Post-RFA: 2 years
<table>
<thead>
<tr>
<th>Pt.</th>
<th>IHC Ki-67</th>
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<td>Study Name</td>
<td>n</td>
<td>FU</td>
<td>CR-IM</td>
<td>CR-D</td>
<td>CR-HGD</td>
<td>Buried Glands</td>
</tr>
<tr>
<td>--------------------------------</td>
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<tr>
<td>AIM-II Trial</td>
<td>61</td>
<td>30 mo</td>
<td>98.4%</td>
<td>--</td>
<td>--</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>60 mo</td>
<td>92%</td>
<td>--</td>
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<tr>
<td>AIM-LGD</td>
<td>10</td>
<td>24 mo</td>
<td>90%</td>
<td>100%</td>
<td>--</td>
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<tr>
<td>HGD Registry</td>
<td>92</td>
<td>12 mo</td>
<td>54%</td>
<td>80%</td>
<td>90%</td>
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<tr>
<td>AMC-I</td>
<td>11</td>
<td>14 mo</td>
<td>100%</td>
<td>100%</td>
<td>--</td>
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<tr>
<td>AMC-II</td>
<td>12</td>
<td>14 mo</td>
<td>100%</td>
<td>100%</td>
<td>--</td>
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<tr>
<td>AMC Long-term FU</td>
<td>23</td>
<td>52 mo</td>
<td>100%</td>
<td>100%</td>
<td>--</td>
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<tr>
<td>Comm Registry</td>
<td>429</td>
<td>20 mo</td>
<td>77%</td>
<td>100%</td>
<td>--</td>
<td>None</td>
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<tr>
<td>EURO-I</td>
<td>24</td>
<td>15 mo</td>
<td>96%</td>
<td>100%</td>
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<tr>
<td>EURO-II</td>
<td>119</td>
<td>12+ mo</td>
<td>91%</td>
<td>96%</td>
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<td>Emory</td>
<td>27</td>
<td>&lt;12 mo</td>
<td>100%</td>
<td>100%</td>
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<td>Dartmouth</td>
<td>25</td>
<td>20 mo</td>
<td>78%</td>
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<td>None</td>
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<tr>
<td>Henry Ford</td>
<td>66</td>
<td>varied</td>
<td>93%</td>
<td>--</td>
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<td>None</td>
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<tr>
<td>Mayo</td>
<td>63</td>
<td>24 mo</td>
<td>79%</td>
<td>89%</td>
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<td>None</td>
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<td>LGD</td>
<td>39</td>
<td>24 mo</td>
<td>87%</td>
<td>95%</td>
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<td>HGD</td>
<td>24</td>
<td>23 mo</td>
<td>67%</td>
<td>79%</td>
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<td>None</td>
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<tr>
<td>AIM RCT (primary)</td>
<td>127 (RFA 84)</td>
<td>12 mo</td>
<td>77% (83%)</td>
<td>86% (92%)</td>
<td>--</td>
<td>5.1%</td>
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<tr>
<td>Long-term FU</td>
<td>106</td>
<td>24 mo</td>
<td>93%</td>
<td>95%</td>
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<td>3.8%</td>
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<tr>
<td>RFA/ER vs. SRER RT</td>
<td>47</td>
<td>24 mo</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>RFA/ER</td>
<td>22</td>
<td>22 mo</td>
<td>96%</td>
<td>96%</td>
<td>--</td>
<td>None</td>
</tr>
<tr>
<td>SRER</td>
<td>25</td>
<td>25 mo</td>
<td>92%</td>
<td>100%</td>
<td>--</td>
<td>8.0%</td>
</tr>
</tbody>
</table>
Barrett’s: Whom to treat

- High grade dysplasia
- Low grad dysplasia
- Long Segment Barrett’s: ?
- Patients “at risk” ??
Confocal Laser Endomicroscopy

Optical Biopsy

- En-face view
- In-vivo
- Microscopic
- Minimally invasive
- Instantaneous imaging

Physical Biopsy

- Transverse view
- Ex-vivo
- Microscopic
- Invasive
- Delayed imaging
Confocal Microscopy for IM surveillance

Sensitivity for neoplasia detection

- Multi-center, randomized controlled trial, 101 patients, 2 arms
- Sensitivity for neoplasia detection
  - WLE or NBI: 68% (x2)
  - pCLE or WLE or NBI: 76% (x1.7)


WLE: White Light Endoscopy
NBI: Narrow Band Imaging

Intestinal metaplasia
High grade dysplasia
Adenocarcinoma
pCLE: Normal
pCLE: IM
pCLE: HGD
pCLE: EAC
EAC Management Then: pre- 2009

- Dysplasia and Early Cancer
Ablation Depth Control

Micro-array at Tissue Interface

RFA depth
Endoscopic Mucosal Resection

15 minutes...Outpatient
Treatment of Early Cancers

- 92% 5 yr survival = surgery
- Success requires:
  - eradication of Barrett’s
  - surveillance
Summary

- Acid reflux = GERD
- GERD not = Barrett’s
- Barrett’s: small percentage progress
- Barrett’s: treatable
- Early cancers: curable (>92%)