The Spectrum of GERD
Implications for Assessment and Management

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Issues in GERD

• Non-erosive Reflux Disease (NERD)
• Functional heartburn
• What are the limits of GERD?
• Extraesophageal GERD
• Barrett's esophagus

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NERD is important

- Common
  - 60% + of all GERD
- Impairs QoL
  - At least as severely as ERD and complicated GERD
- Responds to therapy
  - Especially, if exclude functional heartburn
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3,000 random sample
Kalixanda, Sweden
Symptoms EGD in 1,000

- Symptomatic GERD: 40%
  - NERD: 75.5%
  - Esophagitis: 24.5%
- Barretts: 1.6%
  - Esophagitis: 15.5%
  - Symptoms: 40%
  - Esophagitis 15.5%
  - Symptomatic 63.2%
  - Asymptomatic 36.8%

(Fromkasten et al., Scand J Gastroenterol. 2005; 40: 275-85)

2,760 Individuals
Japan
Evaluated symptoms EGD in ALL

GERD: 17.9%
Esophagitis and/or symptoms

- Symptomatic GERD: 12.7%
  - NERD: 10.7%
  - Esophagitis: 2%
- Esophagitis: 7.1%
  - Symptomatic 1.8%
  - Asymptomatic: 5.3%

(Frommelt et al., Scand J Gastroenterol. 2010; 45: 1053-9)

Symptom relief after 4 weeks*
in NERD patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Complete absence of heartburn (% 95% CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole, 20mg</td>
<td>95/205 (46.3%, 39-53%)</td>
</tr>
<tr>
<td>Omeprazole, 10mg</td>
<td>62/199 (31.1%, 25-38%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>14/105 (13.3%, 7-20%)</td>
</tr>
</tbody>
</table>

* CI = confidence interval


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Predictors of NERD vs. ERD
- NERD
  - Female
  - Hp +
  - More education
    Labenz et al., Am J Gastroenterol 2004; 99: 1652-8
  - Low BMI
  - Non-smoker
  - No HH
  - Severe gastric atrophy
    Fujiwara et al., Am J Gastroenterol 2005; 100: 754-8

- ERD
  - Male
  - BMI
  - Regular alcohol
  - Smoker
  - GERS > 1 year
    Labenz et al., Am J Gastroenterol. 2004; 99: 1652-8

NERD is not homogenous
- Microscopic GERD
- The "sensitive esophagus"
- Functional heartburn

NERD is not homogenous

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Is most NERD minimal change esophageal reflux disease (MERD)?

- Minimal-change esophagitis on high-resolution endoscopy ± chromoendoscopy
- Histological findings on biopsy
  - Lengthened papillae
  - Basal cell hyperplasia
  - NERD: 27/39
  - Controls: 8/39

Mechanisms of symptom production in NERD

- Microscopic esophagitis
- Visceral hypersensitivity
- Sustained longitudinal esophageal contractions
- Abnormal tissue resistance
  - Dilated intercellular spaces

1. What is the pathology of the AET + and SI + groups?
2. What symptoms correspond to microscopic GERD?
3. How do symptoms arise in functional heartburn?
4. Does FH really belong in GERD?
Functional heartburn

- A functional disorder
- What of the role of non-acid reflux?
  - .... unresolved

Predictors of functional heartburn vs. pH + NERD

- Functional heartburn
  - Longer history of heartburn
  - More chest pain
  - Increased somatization
  - Increased autonomic responses to acid infusion

- No Difference
  - QoL
  - Demographics
  - Acid sensitivity
  - HH prevalence
  - Hp prevalence

Interaction between:
- Luminal stimulus
- Central factors
- Local reflexes

Fass and Tougas, Gut 2002; 51: 885-92
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Predictors of success following laparoscopic fundoplication

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio* (95% CI)</th>
<th>Wald's p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive pH score</td>
<td>8.2 (2.7-25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Typical symptom</td>
<td>6.9 (2.4-20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Good response to PPI</td>
<td>4.5 (1.6-12)</td>
<td>&lt;0.004</td>
</tr>
</tbody>
</table>


Functional heartburn

- AET normal; No symptom-reflux association
- No response to PPI
- Not surgical candidates
- Significant overlap with:
  - IBS
  - FD
  - NCCP

Is this really GERD?

Role of DGER in “resistant” GERD

- 65 patients with persistent heartburn on full-dose PPI
  - 51% had persistent esophagitis
- On combined pH/Bilitec recordings:
  - 7 (11%) had abnormal acid exposure
  - 25 (38%) had abnormal DGER
  - 17 (26%) had combined acid and DGER
- Esophagitis had more DGER but not acid

Tack et al., Am J Gastroenterol. 2014; 99: 981-9
NERD: management issues

- In the absence of alarm symptoms, can treat empirically with a PPI
- About 30% will have a permanent remission
- Most of the rest can be managed with on-demand therapy
  - Onset of action and duration of therapy will be important!

What are the limits of GERD?
When does occasional heartburn become a disease?

- Can we define GERD clinically?
- Natural history
- Does detection matter?
- Are we creating a disease?

999 from a community sample
Kalixanda, Sweden
Symptom frequency
QoL by SF-36

<table>
<thead>
<tr>
<th>Frequency heartburn/regurg</th>
<th>Prevalence (%)</th>
<th>Clinically relevant ↓ in QoL (dimensions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>6</td>
<td>8/8</td>
</tr>
<tr>
<td>Weekly</td>
<td>14</td>
<td>5/8</td>
</tr>
<tr>
<td>&lt; Weekly</td>
<td>20</td>
<td>1/8</td>
</tr>
</tbody>
</table>

Ronkainen et al., Aliment Pharmacol Ther. 2006; 23: 1725-33
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3,200 primary care patients
France
Heartburn/regurgitation: 10.1%

- Male: 11.1%
- Female: 9.3%

Weekly symptoms in 72.8%
QoL declined as frequency↑

Bruley des Varannes et al., Gastroenterol Clin Biol. 2006; 30: 364-70

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GERD in China

- 16,091 individuals in Shanghai, Beijing, Xi’an, Wuhan and Guangzhou surveyed re GI symptoms
  - 3.1% had GERD by symptoms
- 1030 subjects in Shanghai had endoscopy
  - 6.5% had esophagitis

Zhao et al., Aliment Pharmacol Ther. 2010; 32: 560-72
He et al., BMC Gastroenterol. 2010; 10: 94

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GERD in China (2)

- 1200 adults in Shanghai
  - GERD: 6.2% by symptoms
    - Associated with:
      - Obesity
      - Urban dwelling
  - 2022 patients with upper GI symptoms
    - BE in 21 patients (1.0%)  
    - Associated with age and reflux esophagitis

Ma et al., Dis Esophagus 2009; 22: 317-22
Xiong et al., J Dig Dis. 2010; 11: 83-7
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1760 randomly sampled
Malmo, Sweden
Symptoms on scale 1–7
QoL on PGWB scale

Symptom score ≥3 (mild)
Clinically meaningful ↓ in QoL

PGWB, psychological general well-being
Wiklund I et al., Am J Gastroenterol. 2006; 101: 18–28

Natural history
NERD 0–30% → Esophagitis
Esophagitis 1–22% → Severe esophagitis
Esophagitis 1–13% → Barrett's

• Was all NERD truly NERD?
• Did esophagitis hide BE?

Fullard M et al., Aliment Pharmacol Ther. 2006; 24: 33–45

Progression in ProGERD

Labenz et al., Am J Gastroenterol. 2006; 101(11):2457–62

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Progression in ProGERD (2)

Heartburn
- Frequent, severe symptoms
- Impaired QoL

GERD
- Gender
- Age
- BMI
- Social factors
- Familial/genetic
- Psyche

Functional heartburn

NERD

Esophagitis

Barrett's

Extra-esophageal, supra-esophageal GERD
- Laryngitis
- Cough
- Asthma
- Sinusitis
- Aspiration
- Tracheal stenosis
- Globus, throat clearing
- Sleep disturbance and sleep apnea

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Laryngitis

- Laryngoscopy
- Gastroscopy
- pH study
  - Not specific for GERD-related laryngitis
  - Response to PPI disappointing in controlled trials
  - Dose increment not helpful

Qadeer et al., Am J Gastroenterol. 2006; 101: 564-54
Vaezi et al., Am J Gastroenterol. 2004; 99: 777-85
Vaezi et al., Laryngoscope 2006; 116: 254?60

34

Non-acid reflux

72 patients with GERD-associated laryngeal symptoms

Aggressive PPI for 4 months

- Responders 65%
- Non-Responders 35%, n=25

Fundoplication

- 10
  - 1 Improved
No Fundoplication

- 15
  - 1 Improved

Swoger et al., Clin Gastroenterol Hpatol. 2006; 4: 433-41

35

Cough and GERD

- Micro-aspiration
  - Acid
  - Non-acid refluxate
  - Reflex activation

36

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Meta-analysis of primary outcome (clinical failures)

Meta-analysis of cough scores at end of intervention

Cochrane

- There is insufficient evidence to definitely conclude that GERD treatment with PPI’s is beneficial for cough associated with GERD in adults

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Non-traditional reflux and cough

Sifrim, D et al., Gut 2005; 54: 449-454

Asthma

- Difficult-to-control asthma
  - GERD symptoms and objective evidence of GERD common

Leggett et al., Chest 2005; 127: 1227-31

Percentage of patients with at least one exacerbation or at least one moderate-to-severe exacerbation of asthma with lansoprazole, 30 mg bid, or placebo bid

Littner et al., Chest 2005; 128: 1129-130

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Scleroderma and GERD

- GERD very common
- Often silent
- Low (absent) LESP + impaired peristaltic amplitude
  conspire to promote GERD and impair clearance
  - Complications
  - Adenocarcinoma

The Barrett's dilemma

- Very common (2% in general adult population)
  - Many asymptomatic
- A premalignant condition
  - But only for a very small minority
- Will not affect mortality from esophageal adenocarcinoma by screening the adult population or even all with GERD
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How do we proceed?

- Incidence of esophageal adenocarcinoma has risen at an alarming rate and is now on the rise in Asian populations
- Patients with Barrett's rarely develop esophageal adenocarcinoma
- 95% of esophageal adenocarcinomas arise in individuals without a prior diagnosis of Barrett's

Risk factors for Barrett's and adenocarcinoma

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=190)</th>
<th>Controls (n=190)</th>
<th>OR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol consumption per week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 drink</td>
<td>28 (15%)</td>
<td>83 (44%)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>9 (17%)</td>
<td>19 (20%)</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>6–10</td>
<td>5 (10%)</td>
<td>8 (9%)</td>
<td>2.35</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>6 (12%)</td>
<td>3 (3%)</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Smoker (current or former)</td>
<td>41 (22%)</td>
<td>53 (52%)</td>
<td>2.15</td>
<td>0.0374</td>
</tr>
<tr>
<td>Coffee consumption</td>
<td>42 (72%)</td>
<td>77 (77%)</td>
<td>0.9</td>
<td>0.8794</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>28 (52%)</td>
<td>48 (69%)</td>
<td>2.06</td>
<td>0.16</td>
</tr>
<tr>
<td>1 y ago</td>
<td>38 (62%)</td>
<td>54 (74%)</td>
<td>1.38</td>
<td>0.494</td>
</tr>
<tr>
<td>5 y ago</td>
<td>29 (53%)</td>
<td>47 (69%)</td>
<td>1.21</td>
<td>0.5853</td>
</tr>
<tr>
<td>10 y ago</td>
<td>27 (49%)</td>
<td>29 (37%)</td>
<td>2.01</td>
<td>0.0311</td>
</tr>
<tr>
<td>20 y ago</td>
<td>23 (38%)</td>
<td>16 (19%)</td>
<td>3.16</td>
<td>0.0046</td>
</tr>
<tr>
<td>Family hx of BE or EAC/EGJAC</td>
<td>14 (24%)</td>
<td>5 (5%)</td>
<td>4.4</td>
<td>0.0038</td>
</tr>
</tbody>
</table>

Can we predict progression?
Genetic markers

- Three transition points:
  - GERD
  - Barrett's
  - Adenocarcinoma

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Genetics

- Three issues:
  - GERD in general
  - Barrett’s
  - Adenocarcinoma

Screen followed by surveillance?

- Current health economics evidence is likely to have provided optimistic cost-effectiveness estimates and is not sufficient to support introduction of endoscopic BE screening programs among GERD patients
- The evidence does not adequately incorporate novel (endoscopic) treatments and the potential for (clinical, endoscopic, or biomarker-based) risk stratification of surveillance

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Barrett’s management issues

- Full dose acid suppression for life
- Effect on natural history
- Endoscopic interventions
  - Endoscopic mucosal resection
  - Endoscopic mucosal dissection
  - Photo-dynamic therapy
  - “Halo” balloon
- Surgery

GERD management issues

- Role of endoscopic anti-reflux procedures for those with chronic, incompletely responsive, anatomically-defective disease
- Motility/sensation modulating agents for functional heartburn and overlap symptoms

GERD management issues (2)

- For occasional heartburn: symptomatic treatment with over-the-counter medications (including PPI’s, where available)
- For GERD
  - NERD and low-grade esophagitis: PPI, initially full dose course followed by on-demand
  - Advanced esophagitis and Barrett’s: continuous full dose PPI
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GERD management issues (3)

• Issues in choosing a PPI:
  • Onset of action
  • Duration of action
  • Side effects
  • Drug interactions
  • Cost

Key points

• We need more information on the risk of progression from GERD to BE and adenocarcinoma; Biomarkers of risk need to be identified
• Proton pump inhibitors have become the standard of medical care in GERD
• Surgery has a role in selected cases but should not be advocated in functional heartburn and with caution in “non-responders”
• NERD is important, common, impairs QoL and responds to therapy
• NERD is not homogeneous and may include:
  • Microscopic GERD
  • The “sensitive esophagus”
  • Functional heartburn
• The true spectrum of extra-esophageal GERD continues to be defined