The Management of PPI Refractory Gastro-Esophageal Reflux Disease

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Introduction
- GERD definition & terminology
- Classification

Workflow in a pt with atypical CP/reflux
- 1st line investigations - endoscopy
- In the absence of esophageal injury, how do we prove there is reflux?
- Acid suppressants – the 1st line of treatment

Failure of Acid Suppressants
- Shall we persist with acid suppressants?
- Other drugs
- Is surgery an option?
Why is GERD a significant problem?

USA Prevalence Study

Locke et al 1997
How important an issue is GERD/NERD locally?

Singapore Community Survey

- Jurong Estate
- Enquiring about reflux symptoms
- 1994 – 4.6%
- 2000 – 10.5%

Increasing incidence that indicates we are catching up with rates in the West

Ho KY et al. Amer Journ Gastroenetrol 1998
Definitions & Classification
(circa. Montreal)

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Esophageal syndromes

- Symptomatic syndromes
  - Typical reflux syndrome
  - Reflux chest pain syndrome

- Syndromes with esophageal injury
  - Reflux esophagitis
  - Reflux stricture
  - Barrett’s esophagus
  - Adenocarcinoma

Extra-esophageal syndromes

- Established association
  - Reflux cough
  - Reflux laryngitis
  - Reflux asthma
  - Reflux dental erosions

- Proposed association
  - Sinusitis
  - Pulmonary fibrosis
  - Pharyngitis
  - Recurrent otitis media
It’s burning!

- 43yr old Female
- No significant medical history
- Episodes of heartburn and a “sourish” sensation
- Worse when stressed (vague relationship)
- Physical examination unremarkable

What would u do...

1. Trial of acid suppression
2. Send her for an OGD
3. ECG/CXR
Which acid suppressant to use?

Normal zone is defined as intraesophageal pH <4 for 0–4.2% of the time over 24 hours.

<table>
<thead>
<tr>
<th>Time pH &lt;4 (minutes)</th>
<th>Pre-treatment</th>
<th>Omeprazole treatment</th>
<th>Ranitidine treatment</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0</td>
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<td>80</td>
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<td>160</td>
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<tr>
<td>200</td>
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</tr>
</tbody>
</table>

** p <0.01 versus pre-treatment
ns, not significant versus pre-treatment

Ruth et al 1988
1. Patient with burning retrosternal discomfort or pain (heartburn)

2. Alarm features?
   - yes → 6. Upper GI endoscopy ± biopsy
   - no → 3. Trial of proton pump inhibitor (PPI)

3. Trial of proton pump inhibitor (PPI)
   - no → 4. Heartburn resolved?
     - yes → 5. Gastroesophageal reflux disease: titrate PPI therapy
     - no → 6. Upper GI endoscopy ± biopsy

6. Upper GI endoscopy ± biopsy

There is no convention for the dosage, duration, or specific drug to be used in a proton pump inhibitor (PPI) trial for heartburn, making it reasonable to treat with a standard once daily dose for 2 weeks.
Once a satisfactory response has been achieved, the PPI dosage should be reduced to the lowest amount that is still associated with a satisfactory treatment effect.

1. **Patient with burning retrosternal discomfort or pain (heartburn)**

2. **Alarm features?**
   - no → 3. **Trial of proton pump inhibitor (PPI)**
   - yes → 6. **Upper GI endoscopy ± biopsy**

3. **Trial of proton pump inhibitor (PPI)**

4. **Heartburn resolved?**
   - yes → 5. **Gastroesophageal reflux disease: titrate PPI therapy**
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RF Diagnostic Algorithms Amer Journ Gastroenterol 2010; 105
Patient with burning retrosternal discomfort or pain (heartburn)

1. Patient with burning retrosternal discomfort or pain (heartburn)
2. Alarm features?
   - Yes: Upper GI endoscopy ± biopsy
   - No: Trial of proton pump inhibitor (PPI)
3. Trial of proton pump inhibitor (PPI)
4. Heartburn resolved?
   - Yes: Gastroesophageal reflux disease: titrate PPI therapy
   - No: If insufficient response is achieved with standard dose PPI, this should be increased to twice daily for at least 2 weeks before considering it a treatment failure.

RF Diagnostic Algorithms Amer Journ Gastroenterol 2010; 105
Omeprazole 20mg BD

- No response

Gastroscopy
Patient with burning retrosternal discomfort or pain (heartburn)

2. Alarm features?
   - No
   - Yes

6. Upper GI endoscopy ± biopsy

7. Any abnormality identified?
   - No
   - Yes

8. LA A–D esophagitis, eosinophilic esophagitis
Reflux Esophagitis

Direct physical evidence of acid reflux

Lundell et al 1999; published with permission from Professor G Tytgat and Professor J Dent
Dilated Intercellular Spaces

New modality for increasing sensitivity in the diagnosis of refluxate induced damage
Definitions & Classification
(circa. Montreal)

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Symptomatic syndromes
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Syndromes with esophageal injury
- Reflux esophagitis
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- Barrett’s esophagus
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Established association
- Reflux cough
- Reflux laryngitis
- Reflux asthma
- Reflux dental erosions

Extra-esophageal syndromes

Proposed association
- Sinusitis
- Pulmonary fibrosis
- Pharyngitis
- Recurrent otitis media
Acid suppression remains the cornerstone in esophagitis caused by reflux

Chiba et al 1997
The evidence for PPIs in Esophagitis

<table>
<thead>
<tr>
<th>Esophagitis healing (all severities)</th>
<th>PPIs are superior to placebo: 83% vs 18% at 8 wk, NNT = 1.7 (^{21})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPIs dose-response curve exhibits a plateau: low vs standard dose, NNT = 10 at 4 wk; standard vs high or split dose, NNT = 25 at 4 wk (^{21})</td>
</tr>
<tr>
<td></td>
<td>PPIs are superior to H(_2)RAs: 84% vs 52%, (^{20}) RR = 0.51 (^{21})</td>
</tr>
<tr>
<td></td>
<td>H(_2)RAs show no dose-response curve (standard vs high or split dose) (^{21})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heartburn resolution (patients with esophagitis)</th>
<th>PPIs are superior to placebo: 56% vs 8% at 4 wk, NNT = 2–3 (^{22})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPIs show no dose-response curve: low vs standard dose, 75% vs 79% at 4 wk; standard vs high or split dose, 73% vs 76% at 4 wk (^{21})</td>
</tr>
<tr>
<td></td>
<td>PPIs are superior to H(_2)RAs: 77% vs 48% at 4–12 wk (^{23})</td>
</tr>
<tr>
<td></td>
<td>H(_2)RAs are superior to placebo: 56% vs 45% at 12 wk (^{24})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintenance of esophagitis healing or symptom control (6-12 months)</th>
<th>PPIs are superior to placebo for maintaining healing: 93% vs 29% (^{28})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-dose PPI therapy is sufficient to maintain endoscopic remission in 35–95% of patients with esophagitis (^{20})</td>
</tr>
</tbody>
</table>
Omeprazole 20mg BD
- No response

Endoscopy
- Normal
- No esophagitis

Nexium 20mg BD
- Some mild, transient improvement
- Do I need to take this lifelong?
- It’s expensive
- Are there side effects?
What are the issues?

**Heartburn & GERD**
- Acid suppression with a PPI and titrate dosing
- Endoscopy if there are “red flags” or non-responsive to PPI

**Is acid the problem?**
- In absence of overt esophagitis, can we prove that acid is the cause?
pH or impedance-pH monitoring is performed after withholding PPI therapy for 7 days to obtain a meaningful assessment of esophageal acid exposure and to provide the greatest chance of finding a positive association between heartburn episodes and reflux events.
24hr pH testing
48hr Wireless pH testing
Reason for Study: Reflux oesophagitis

Study Comments
Increased acid exposure; all acid regurgitation (29 episodes of mild to moderate) DID occur at times of acid reflux events.
What are the issues?

Heartburn & GERD
- Acid suppression with a PPI and titrate dosing
- Endoscopy if there are “red flags” or non-responsive to PPI

Is acid the problem?
- In absence of overt esophagitis, can we prove that acid is the cause?

What if there is no acidic reflux?
- Is all reflux acidic?
- If not, how do we document non-acidic reflux?
pH-Impedance Testing
Measuring technique

- Use a catheter with metal rings
- A small electrical current is used to measure the impedance between the 2 rings

Patient safe

low electrical current
Impedance signals

Animation

[Graphs showing impedance signals labeled IMP and PRES]
Impedance signals

Baseline Air Bolus Contraction Baseline

Bolus entry .... exit
Gastric reflux

- \( \backslash \) \( \backslash \) shaped waveform
Extent of reflux

Type of reflux
Ambulatory 24hr pH- impedance-manometry
reflux  cough

Sifrim et al. Gut

impedance
pH oes
pH fundus
manometry

weakly acidic reflux (pH 5.6)
cough

Medical Measurement Systems
Does Impedance add value – i.e. does it increase yield?

Comparative study between pH and pH-Impedance
• 60 patients with reflux symptoms
• Off PPI
• Underwent pH and impedance testing
• Yield compared between acid reflux and all reflux events


The proportion of patients with a positive SAP (≥95.0%) varied between 62.5% and 77.1%, depending on the definition of reflux episodes. When both pH and impedance parameters were used to identify reflux, a higher proportion of patients had a positive SAP than with pH alone (77.1% vs 66.7%, p < 0.05). Symptom association analysis for acidic and weakly acidic reflux separately did not result in a higher yield than analysis with all reflux episodes pooled, regardless of pH.

In patients off proton pump inhibitor, the addition of impedance monitoring to esophageal pH monitoring leads to an increase in the proportion of patients in whom an association between reflux episodes and symptoms can be identified.
**pH-Impedance measurement**

<table>
<thead>
<tr>
<th>Document ALL reflux</th>
<th>Correlation with symptoms</th>
<th>Utility</th>
</tr>
</thead>
</table>
| • Duration of lower esophageal acid exposure (intensity)  
• No of events (frequency) | • Match symptoms with reflux events  
• Symptom Index (SI)  
• Symptom Association Probability (SAP) | • Acidic reflux  
• Non-acidic reflux  
• Air movement (belching)  
• Explore correlates with extra-esophageal symptoms |
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The treatment & diagnostic conundrum

• Proven reflux – esophagitis on endoscopy or positive reflux testing

• Persistent symptoms despite acid suppression with PPIs

What are the options open to us?

1. Persist with acid suppression
2. Anti-reflux agents
3. Prokinetics
4. Surgery
# Risks of long-term acid suppression

<table>
<thead>
<tr>
<th>Potential risks of hypochlorhydria (trophic, absorptive)</th>
<th>Risk magnitude/possible consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypergastrinemia-induced carcinoid tumors</td>
<td>Not demonstrated in humans\textsuperscript{113}</td>
</tr>
<tr>
<td>Accelerated progression of atrophic gastritis/gastric cancer with concomitant <em>H pylori</em> gastritis\textsuperscript{115}</td>
<td>No documentation of an increase in atrophic gastritis and no basis to recommend testing or treatment for <em>H pylori</em> before long-term PPI use\textsuperscript{116}</td>
</tr>
<tr>
<td>Formation of gastric fundic gland polyps\textsuperscript{168}</td>
<td>Odds ratio of 2.2 for developing fundic gland polyps within 1–5 years,\textsuperscript{168} negligible, if any, risk of dysplasia</td>
</tr>
<tr>
<td>Vitamin B\textsubscript{12} malabsorption</td>
<td>Some patients show decreased vitamin B\textsubscript{12} levels after years of acid inhibition,\textsuperscript{113} case reports (2) of clear deficiency\textsuperscript{114}</td>
</tr>
<tr>
<td>Calcium malabsorption</td>
<td>Nested case-control study of UK patients older than 50 years; adjusted odds ratio of 1.44 (95% confidence interval, 1.30–1.59) of hip fracture with PPI use longer than 1 year\textsuperscript{122}</td>
</tr>
<tr>
<td>Iron malabsorption</td>
<td>Poor response to oral iron supplement absorption in 2 iron-deficient individuals improved after cessation of omeprazole; no clear clinical relevance\textsuperscript{169}</td>
</tr>
</tbody>
</table>

| Potential risks of hypochlorhydria (infectious)         | PPI use is independent risk of *C difficile* diarrhea in antibiotic users, odds ratio of 2.1 (95% confidence interval, 1.2–3.5)\textsuperscript{120} |
|----------------------------------------------------------| Nested case-control analysis, adjusted odds ratio for pneumonia with PPI use of 1.73 (95% confidence interval, 1.33–2.25)\textsuperscript{121} |

| Generic pharmacologic risks                              | Data on PPI use and increased gastric N-nitrosamine remain uncertain and the risk of cancer is speculative\textsuperscript{113} |
|----------------------------------------------------------| Based on 345 accidental exposures compared with 787 controls, no observed increased teratogenicity\textsuperscript{123} |
| Safety in pregnancy (omeprazole crosses placenta and is pregnancy safety category C; other PPIs are category B) Drug-drug interactions; PPIs metabolized by cytochrome P450 and may induce or inhibit drug metabolism (phenytoin, warfarin, and so on) Anaphylaxis Acute interstitial nephritis Pancreatitis | Clinically significant PPI drug-drug interactions are rare (<1/million prescriptions)\textsuperscript{124} |

One case report with lansoprazole\textsuperscript{125} 64 cases worldwide, partially reversible (one case requires dialysis, no deaths), estimated risk 1/12,500 patient-years of therapy\textsuperscript{126,127} Population-based case-control study adjusted odds ratio of 3.2 (95% confidence interval, 1.4–7.4\textsuperscript{128} |
Prokinetics

Cisapride
• Withdrawn because of arrythmias

Mosapride
• Possible agent

Metoclopramide
• No significant efficacy data

NO PROVEN ROLE FOR PROKINETICS IN GERD!
Anti-Reflux Medication

GABA-agonist
- Baclofen 10-20mg TDS
- REDuces TLESRs by 40-60%
- Overall reflux by 40%
- CNS side-effects
  1. Dizziness
  2. Somnolence
  3. weakness
- Short t-1/2 of 3-4hrs
**GABA-agonist (1)**

Lesogabaran
- Peripherally acting agent – less CNS side-effects
- Phase 2a trials
- Show that when used concurrently with PPIs, markedly improve symptoms

**GABA-agonist (2)**

Arbaclofen placabril
- R-isomer of baclofen and a pro-drug
- Long t-1/2 of 12hrs
- Therefore long-lasting suppression on TLESRs

**CB1 (cannabinoid receptor)**

- Rimonabant (CB1 antagonist)
- D9-THC (CB1/2 agonist)

**mGluR5**

Glutamate as NT at vagal afferent terminals
Allosteric inhibitors at mGluR5 receptor
- ADX10059
- AZD2516
- AFQ056

**TLESRs**
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
Anti-reflux Surgery

Nissen fundoplication

Toupet procedure
Endoscopic Fundoplication
EsophyX
So is there a role for anti-reflux surgery?

Grade A: strongly recommended based on good evidence that it improves important health outcomes

I. When antireflux surgery and PPI therapy are judged to offer similar efficacy in a patient with an esophageal GERD syndrome, PPI therapy should be recommended as initial therapy because of superior safety.

II. When a patient with an esophageal GERD syndrome is responsive to, but intolerant of, acid suppressive therapy, antireflux surgery should be recommended as an alternative.

Grade B: recommended with fair evidence that it improves important outcomes

I. Antireflux surgery for patients with an esophageal GERD syndrome with persistent troublesome symptoms, especially troublesome regurgitation, despite PPI therapy. The potential benefits of antireflux surgery should be weighed against the deleterious effect of new symptoms consequent from surgery, particularly dysphagia, flatulence, an inability to belch, and postsurgery bowel symptoms.

Grade C: balance of benefits and harms is too close to justify a general recommendation

I. Patients with an extraesophageal GERD syndrome with persistent troublesome symptoms despite PPI therapy should be considered for antireflux surgery. The potential benefits of antireflux surgery should be weighed against the deleterious effect of new symptoms consequent from surgery, particularly dysphagia, flatulence, an inability to belch, and postsurgery bowel symptoms.

Grade D: recommend against, fair evidence that it is ineffective or harms outweigh benefits

I. Antireflux surgery for patients with an esophageal syndrome with or without tissue damage who are symptomatically well controlled on medical therapy.

II. Antireflux surgery as an antineoplastic measure in patients with Barrett's metaplasia.

Grade Insuff: no recommendation, insufficient evidence to recommend for or against

I. The use of currently commercially available endoluminal antireflux procedures in the management of patients with an esophageal syndrome.
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