Extraesophageal Reflux: When Empiric Therapy Doesn’t Work

Andrew Coughlin, MD
Michael Underbrink, MD, FACS
The University of Texas Medical Branch (UTMB Health)
Department of Otolaryngology
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Outline

• Scope of Extra-esophageal Reflux
• Relevant Anatomy and Physiology
• Describe Extra-esophageal Reflux Syndromes
• Workup of Empiric Treatment Failures
• Indications for Surgical Therapy
• Results of Surgical Therapy
• Discuss my approach to the PPI resistant patient
Impact of Reflux

• 25% of adults experience reflux monthly

• 5-10% experience reflux daily

• PPI’s 3rd most prescribed medication
  – $13.6 billion annually 2009
GERD defined as:
“a condition that develops when the reflux of the stomach contents causes Troublesome symptoms and/or complications”

Troublesome:
“adversely affects an individuals well being”
Metaplasia

http://sitemaker.umich.edu/betrnet/significance
Montreal Classification

GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.

- **Esophageal Syndromes**
  - Symptomatic Syndromes
    - Typical reflux syndrome
    - Reflux chest pain syndrome
  - Syndromes with Esophageal Injury
    - Reflux esophagitis
    - Reflux stricture
    - Barrett’s esophagus
    - Adenocarcinoma
  - Established Association
    - Reflux cough
    - Reflux laryngitis
    - Reflux asthma
    - Reflux dental erosions

- **Extra-esophageal Syndromes**
  - Proposed Association
    - Sinusitis
    - Pulmonary fibrosis
    - Pharyngitis
    - Recurrent otitis media

Yuksel et al.
Relevant Anatomy
Esophageal Anatomy

18-22 cm long

- Upper esophageal sphincter
- Striated
- Polymyositis
- Myasthenia gravis

Circular

Longitudinal

Smooth
- Scleroderma
- Achalasia

Lower esophageal sphincter

Nonkeratinizing Stratified Squamous Epithelium
Laryngeal Mucosa

http://www.medicalhistology.us/twiki/bin/view/Main/RespiratorySystemAtlas09
Esophageal Sphincters

• Upper Esophageal Sphincter
  – Inner circular layer associated with cricopharyngeus

• Lower Esophageal Sphincter
  – Opens with peristalsis
  – Resting tone 15-45mm Hg
Physiology of Parietal cell
Empiric Therapy for Patients with Symptoms

• GERD
  – Heartburn
  – Epigastric pain
  – Shortness of Breath
  – Regurgitation
  – Belching
  – Chest Pain

• LPRD
  – Dysphagia
  – Sore Thorat
  – Halitosis
  – Voice Changes
  – Cough
  – Throat Clearing
  – Globus Sensation
Cochran Review on Medical Therapy

• Review of RCT’s (van Pinxteren et al. 2006)
  – PPI’s vs H2-Blockers vs Prokinetic medications

• Studies evaluating empiric therapy (19)
  – PPI significantly better at relieving reflux symptoms \( (RR: 0.37) \)

• Studies evaluating ENRD (17)
  – PPI significantly better at relieving reflux symptoms \( (RR: 0.73) \)
Scrutiny over reflux symptoms

Acid Overproduction

-or-

LES Dysfunction
Should we be using PPI’s so casually?
Fractures (Yu et al.)

- Meta-analysis 10 studies looking at:
  - PPI or H2 blocker usage versus control
  - In general included postmenopausal and older men
  - No RCT’s mainly case control and prospective observational
  - Modest increase risk of fractures (M=F)
    - Hip RR = 1.3
    - Spine RR = 1.56
  - H2 – Blockers not associated with increased risk
Effects on Plavix (Bhatt)

- DB/PC/RCT of Clopidogrel plus PPI or placebo
- Approximately 3800 patients each arm
- Results
  - GI event (1.1% vs 2.9%)
  - Cardiovascular Events (4.9% vs 5.7%)

***No significant increases in the risk of cardiovascular events even in high-risk subgroups
Dependence Issues

- 2009 Reimer et al. (33)
  - Randomized, Double Blinded, Placebo controlled trial of 120 normal patients
    - 12 weeks of placebo
    - 8 weeks of Nexium 40mg/day then 4 weeks placebo
  - Measured GI symptom rating scores (GSRS) weekly
  - Results
    - Both groups similar at baseline
    - Higher GSRS (worse) score at 10, 11, 12 weeks
    - 44% vs 15% reported >1 acid related symptom week 9-12

*If you start a PPI, you may not be able to stop it*
Extra-esophageal Syndromes
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Asthma
Reflux and Asthma Cycle

- Increased Negative Intrathoracic Pressure
- Direct Injury from Reflux
- Increased Cough
- Asthma Exacerbation
Asthma

- Asthma not only is exacerbated by reflux but can also make it worse
  - Steroids and beta agonists relax the LES
Asthma

- Leggett et al.
  - 52 patients with difficult to control asthma
  - Dual Probe pH monitoring
  - 39 patients (75%) had evidence of reflux
    - 55% at distal probe (5cm above LES)
    - 34.6% at the proximal probe (15cm above distal probe)
  - Only 16% of coughing episodes were associated with reflux
Asthma

- American Lung Association Asthma Clinical Research Centers
  - DB/PC/RCT of 412 patients with uncontrolled asthma and no reflux symptoms
  - Nexium 40mg BID versus Placebo for 24 weeks
  - Ambulatory 24 hour pH monitoring at baseline
- Results
  - 40% of patients had asymptomatic reflux
  - No significant difference in asthma exacerbations or PFT’s with treatment
Asthma

- Kiljander et al.
- DB/PC/RCT 770 subjects with moderate to severe asthma
- Nexium 40mg BID vs. Placebo for 16 weeks
- Results
  - Significant improvement in PFT’s in patients with pretreatment nocturnal symptoms and GERD versus patients without pretreatment GERD or nocturnal symptoms
Asthma Recommendation

- Empiric treatment is not helpful unless patients are symptomatic for GERD
- Especially helpful with nocturnal symptoms
- Shoot for lowest effective dose
- If not responsive perform additional workup
Chronic Cough
Chronic Cough

• Present >8 weeks
• 5 most common causes (90% of cases)
  – Postnasal drip
  – Asthma
  – Gastroesophageal reflux
  – Chronic Bronchitis
  – ACE inhibitor
Chronic Cough (Jacobs)

- Triggered by
  - Irritation of the respiratory tract by aspiration
  - Stimulation of an esophageal-bronchial cough reflex (Vagal mediated)
Chronic Cough

• 75% of patients with GER-related cough do not exhibit typical reflux symptoms

• Low specificity of studies to diagnose chronic cough
  – EGD showed only 15% esophagitis in patients with chronic cough (Baldi et al.)

• Success ill-defined
  – Only 35% of patients with abnormal 24 hour pH measurement showed a response to therapy (Ours et al.)
Treatment Chronic Cough

• Poe et al.
  – 79% of patients with cough secondary to GER responded to daily PPI

• Baldi et al.
  – 60% resolution of symptoms
  – Lansoprazole 30mg BID for 4 weeks then BID or daily therapy for 12 weeks
  – No difference between groups
Chronic Cough Recommendation

- Treat with BID PPI for 12 weeks and if no improvement
  - Reassess for PND/Asthma/Bronchitis/etc.
  - Move forward with additional studies to determine if reflux is present
Laryngitis
Laryngitis

• Symptoms
  – Hoarseness
  – Globus sensation
  – Dysphagia
  – Cough
  – Mucous production
  – Sore throat
  – Halitosis
  – Throat clearing

• Signs
  – Erythema of mucosa
  – Vocal cord edema
  – Interarytenoid pachydermia
  – Laryngeal mucous
  – Subglottic edema
  – Granulomas
Nonspecific Nature of LPR

- 80-90% of normal patients will have “reflux findings” on laryngoscopy (Milstein et al.)
- Hypopharyngeal reflux can be found in 19-43% of normal volunteers on pH monitoring (Joniau et al.)
- pH probe-documented LPR in 50% despite LPR symptoms in 69% (Koufman et al.)
Differences between GERD and LPRD (Koufman et al)

- Esophagitis is rare in LPRD (25%)
- Daytime vs Nighttime reflux
- UES vs LES
- Short vs Prolonged acid exposure
- Laryngeal vs Esophageal irritation
- BID vs Daily PPI therapy

Position statement by the AAO 2002
Laryngitis Recommendations

• BID PPI for 6 months
• Plus or minus H2-blocker
• Additional studies if patients do not respond
Chest Pain

- Recurring chest pain with **negative cardiac workup**
  - Burning
  - Pressure-like
  - Substernal
  - Occurring with exercise
What makes you think reflux?

- Post-prandial pain
- Continues for hours
- Retrosternal without radiation
- Relieved with antacids
- Pain that disturbs sleep (Yuksel et al.)

***CARDIAC CAUSES RULED OUT***
Therapy for Non-Cardiac Chest Pain

• Achem et al.
  – 36 patients with pH study positive reflux and noncardiac chest pain
  – Omeprazole 20mg vs Placebo
  – Symptoms improvement in 81% vs 6% of patients

• Pandak et al.
  – 37 patients in a crossover study evaluating Omeprazole 40mg BID vs Placebo x 14 days/21 day washout then switch.
  – EGD, Esophageal Manometry, Dual Probe pH evaluation at baseline
  – 71% of patients treated with omeprazole had significant symptoms improvement
  – 95% of patients with proven GER responded
  – Reflux investigations not sensitive and were much more expensive than empiric therapy
Chest Pain
Recommendations

• Empiric treatment with PPI for 2-3 months
• Taper to lowest effective dose for responders
• Additional investigations for non-responders
If patients respond to treatment...Great!!!

If patients fail therapy is it:
Resistant Reflux
or
Something Else
Differential Diagnosis

• Asthma/Cough/Laryngitis
  – Non-acidic reflux
  – Eosinophilic Esophagitis

• Chest Pain
  – Achalasia
  – Strictures
  – Nutcracker esophagus
  – Diffuse esophageal spasm
Workup

- Physiologic Testing
  - EGD
  - 24 hour PH Probe
  - Intraluminal Impedence
  - Esophageal Manometry
  - Upper GI or Barium studies
EGD or TNE

- Direct visualization of the esophagus
- Ability to biopsy for Barrett’s or Strictures
- Does not always show esophagitis in patients with reflux symptoms
Mucosal Breaks

Epithelial slough/erythema adjacent to normal tissue
Eosinophilic Esophagitis

![Concentric Rings](image1)

Linear furrowing occurs in 25-100% of patients

Loss of Vascularity occurs in 93% of patients
EE vs GERD
EE vs GERD
24 hour pH Probe Testing (Dual Probe)

- Reserved for patients who have failed therapy or if diagnosis is unclear
- Ability to
  - Quantify the number and duration of reflux episodes
  - Differentiate between upright and supine reflux
  - Correlate these events with subjective symptoms
- No consensus on what qualifies as LPRD
  - >0 reflux events/hour
  - >4 reflux events/hour
Dual PH Probe Tracing
Intraluminal Impedence (Castell)

- Very helpful in evaluation of non-acidic reflux
- Measures directional electrical resistance changes to gas, liquid or solid bolus in the esophagus
- Measures level of reflux
- Can be used in conjunction with pH monitoring to determine the type of reflux that is occurring
Impedence and pH testing

http://www.nature.com/ajg/journal/v102/n3/fig_tab/ajg2007119f5.html#figure-title
Esophageal Manometry

- Measures
  - Peristalsis
  - Esophageal Sphincter Pressure
- Can reveal motility problems that can cause changes in surgical plan in up to 10% of patients (i.e. subtotal fundoplication)
Manometry Example

Ineffective oesophageal motility

Low amplitude contraction

Non-transmitted contraction
Manometry Diseases

http://www.nature.com/gimo/contents/pt1/fig_tab/gimo20_F2.html
Upper GI Series

- Excellent for anatomic evaluation with regards to the LES and the Hiatus
  - Hiatal Hernias
  - Strictures
  - Shortened esophagus
  - Qualitative Evaluation of esophageal peristalsis
Diffuse Esophageal Spasm
Achalasia

http://www.patient.co.uk/doctor/Achalasia.htm
We have all these tests but what do the surgeons say about offering surgery?
Nissen Fundoplication

• Dr. Rudolf Nissen
• First described in 1950’s
• Laparoscopic Nissen has come into favor (Stefanidis et al)
  – Improved cosmesis
  – Reduced morbidity
  – Decrease hospital stay
  – Decreased respiratory complications
  – Faster recovery
Nissen Procedure

Nissen fundoplication

Normal stomach

After surgery
SAGES Consensus Statement

• GERD diagnosis with one of the following:
  – Mucosal break
  – Barrett’s Esophagus on biopsy
  – Peptic stricture with no malignancy
  – Positive pH-metry

***Grade A recommendation

SAGES: Society of American Gastrointestinal and Endoscopic Surgeons
SAGES Consensus Statement

• pH probe studies (PPI and H2-blocker free interval)
  – Total time with pH<4, 5cm above LES
  – Composite score of:
    • Total esophageal acid exposure (time)
    • Upright acid exposure (time)
    • Supine acid exposure (time)
    • Number of episodes
    • Number of episodes lasting >5min.
    • Duration of longest episode

***Wireless 48 hour monitoring is equivalent
SAGES Consensus Statement

• No recommendation for mandatory preoperative manometry
  – Can identify achalasia or other surgical modifying conditions

• Barium swallow not mandatory but can be helpful to delineate anatomy

• Gastric emptying studies to not help preoperatively, but can identify nerve injuries after the first surgery
SAGES Criteria

• Indications for surgery
  – Failed medical management
  – Opt for surgery instead of medical management despite success
  – Complications of GERD
    • Barrett’s Esophagus
    • Peptic Stricture
  – Have extra-esophagaeal manifestations
Predictors of Success

- Francis et al.
- Retrospective review of 237 patients referred for extraesophageal reflux resistant to therapy
- 27 patients treated with Nissen for objective reflux findings
- EGD, pH monitoring, Impedence, Manometry all performed
- Results
  - 59% at least partial improvement in symptoms
  - Better results in patients with heartburn +/- regurgitation at initial visit, a hiatal hernia, and pH<4 for more than 12% of time on pH monitoring
  - Manometry, Impedence, and EGD did not predict success
Surgery vs PPI Therapy

• Lundell et al.
• Randomized trial of Surgery vs PPI
  – 155 patients in each arm
  – 71 in medical group and 53 in surgical group at 12 yrs
• Reassessed by EGD and symptomatology
• Results
  – 53% of patients treated with surgery in remission
  – 40% of patients treated with medicine in remission
Surgery more effective than medical therapy?

- Primary outcomes:
  - Reflux Specific QOL (GSRS)
  - Heartburn
  - Regurgitation
  - Dysphagia
- 4 RCT studied and over 1200 patients
- Significant improvement in patients treated with Surgery
  - Still true at 3 months and 1 year post-op QOL measures
- Surgery more costly, low complication rate (1.7%), small % patients have persistent dysphagia (4.6%)
- Medical therapy more likely to have persistent heartburn or regurgitation issues
Cost effectiveness study of surgery versus medical therapy

• Thijssen et al.
• Systematic review of cost effectiveness studies
• 4 articles reviewed
  – 2 favored medical management
    • Lower initial costs
    • More symptom free months
  – 2 favored surgical management
    • More expensive
    • More Quality adjusted life years than PPI
• Studies looked specifically at 3rd party
• Ultimately more long term data needed as most is inconclusive
New Therapy on the Horizon

• The real problem is LES dysfunction
• GABA agonists (Baclofen and R-Baclofen)
  – Show excellent response at:
    • Decreasing transient hypotension of the LES
    • Decreasing reflux events
  – Poorly tolerated due to central effects and dosing
• Currently developing peripheral agonists and slow-release drugs
• Good initial results in experimental trials when added to PPI
  • Reduced reflux and heartburn events
Conclusions

• Start with empiric therapy and don’t order expensive tests
  – If patients succeed with PPI therapy → Taper LED
  – If patients fail → Confirm reflux with pH probe or EGD

• Impedence testing/Manometry/Upper GI/Barium Swallow are not predictors of surgical success

• Refer to General Surgeons only if you have documented reflux
References


• Wileman SM, McCann S, Grant AM, Krukowski ZH, Bruce J. Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database Syst Rev. 2010;17:CD003243