Panel – Reflux/LPR
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Nikki Johnston, PhD
Cecile G. Sulman, MD

August 6-9, 2016 | The American Club | Kohler, WI

What’s in store?
• Overview/Introduction – JHB
• Sample adult patients approach – JMB
• Drug Discovery Project – NJ
• Sample pediatric patient approach – CGS
• Algorithmic approach
• Ford, JAMA 2005

The Case for Empiric Therapy

• Benefits of medicine
  • Risks of medicine
  • Inconvenience of medicine
  • Costs of medicine

• Benefits of testing
  • Risks of testing
  • Inconvenience of testing
  • Costs of testing

Has laryngeal reflux and the availability & safety of PPIs made us lazy?
  – A ‘garbage pail’ diagnosis?
  – Provides an easy way to get these patients out of the office
What is the disease evaluation?

- Constellation of non-specific laryngeal inflammatory symptoms
  - Hoarse voice
  - Cough
  - Throat clearing
  - Globus sensation

Reflux Symptom Index
Belafsky PC, Prokesh GR, Koufman JA.
The validity and reliability of the reflux symptom index (RSI). J Voice 2002

> 13 = suggestive of reflux

<table>
<thead>
<tr>
<th>Within the last MONTH, how did the following problems affect you?</th>
<th>0 = no problem</th>
<th>5 = severe problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hoarseness or a problem with your voice</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>2. Clearing your throat</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>3. Excessive throat mucous or postnasal drip</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>4. Difficulty swallowing fluid, liquids, or pills</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>5. Coughing after you ate or after lying down</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>6. Breathing difficulties or choking episodes</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>7. Trouble eating or swallowing</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>8. Sensations of something sticking in your throat or a lump in your throat</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>9. Heartburn, chest pain, indigestion, or stomach acid coming up</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
</tbody>
</table>

What is the disease evaluation?

- Constellation of laryngeal inflammatory signs
  - Laryngeal edema
  - Laryngeal erythema
  - Laryngeal mucus
  - Granulation/granular mucosa
  - Pachydermia/thickened epithelium
Reflux Finding Score
Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux findings score (RFS). Laryngoscope 2001

<table>
<thead>
<tr>
<th>Findings</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal edema</td>
<td>0 = absent</td>
</tr>
<tr>
<td>Vomitor</td>
<td>2 = present</td>
</tr>
<tr>
<td>Uvula</td>
<td>2 = present</td>
</tr>
<tr>
<td>Vocal fold edema</td>
<td>1 = mild</td>
</tr>
<tr>
<td>Vocal fold atrophy</td>
<td>0 = absent</td>
</tr>
</tbody>
</table>

> >7 = suggestive of reflux

Potential Branch Point in Algorithm

• Gold standard testing
  – Laboratory, imaging, or other
  – pH probe for reflux

pH probe testing

• Invasive
  • Controversy in device
    – Single probe, dual probe, NP probe, impedance probe, wireless capsule probe
  • 24 – 48 hour snapshot
    – May not be predictable of a patient’s ‘normal’
• Controversy in interpretation
  – Does presence of acid imply LPR?
  – Does acid exposure cause symptoms?
  – Does the absence of acid imply LPR?
  • Role of impedance-pH monitoring
• Does a positive pH probe predict response?
  – Response to PPI can be variable
Empiric PPI

• Good safety profile of medicine
  – Released as an OTC medicine in 2003
  – …however, data emerging over the last 5-10 years suggest these medicines are not innocuous

• Well tolerated
  – Rare dyspepsia, diarrhea, or allergy (rash)

PPIs are effective at acid suppression
but not perfect…

Risks of PPI therapy

• Related to acid suppression
  – B12 deficiency
  – Pneumonia, enteric infections (C. difficile)
  – Malabsorptions - calcium (osteopenia), magnesium

• Physiologic response to acid suppression
  – Gastric fundic gland hyperplasia (polyps)
  – Hypergastrinemia

• Pharmacodynamic interactions
  – clopidogrel
  – warfarin
  – phenytoin, etc

• Other
  – Increased MI
  – Renal failure
  – Dementia
Responsible use of Empiric PPI Treatment

- Make sure patient understands that this is empiric treatment
  - Inherent limitations of not utilizing objective testing

- Don’t give PPIs to everyone that walks into your clinic that is hoarse or has a throat complaint
  - Hopefully not a problem with otolaryngologists

- Define a time course of empiric therapy and follow up with patient
  - 6-12 weeks depending on symptoms and signs

Responsible use of Empiric PPI Treatment

- Be willing to challenge the diagnostic hypothesis in non-responders
  - Don’t just keep increasing acid suppression without a defined goal
  - This would be a good time to think about objective testing (pH testing)

Responsible use of Empiric PPI Treatment

- Titrate dose down to effect
  - Most long-term risks are stratified to dose

- Define endpoint (or at least think about it) in responders
  - This would be a good time to think about objective testing (pH probe), especially in those that you are considering long term treatment
  - Anti reflux surgery?
    - Especially for life threatening complications of reflux such as airway stenosis or severe asthma

- Discuss possible calcium/vitamin D supplementation and/or osteopenia evaluation
  - Defer to internist
The Future

• Likely evolve away from acid suppressive approach
  – Too much long term ‘baggage’
  – Does nothing for reflux, only for acid

• Suspect there will be more operations –
  endoscopic ‘minimally invasive’ and laparoscopic

• Need good data to properly counsel our patients
Reflux Testing 2016

Jonathan M. Bock, MD, FACS
Associate Professor
Division of Laryngology & Professional Voice
Department of Otolaryngology & Communication Sciences
Medical College of Wisconsin

What clinical complaint most often makes you think of reflux testing as an option?

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or Open poll in your web browser
What is the most common test you (or your GI colleagues) perform for reflux testing?

A. Don’t do it
B. Restech-pH (nasopharyngeal probe)
C. Bravo
D. Barium Esophagram
E. Dual pH-Multichannel Intraluminal Impedance

Symptom-Based “LPR” Algorithm

- Base your first treatment on the predominant symptom and history, not as much the exam findings
- What symptom are we trying to treat?
  - Hoarseness?
  - Cough?
  - Globus?
  - Throat clearing?
**Why do reflux testing?**

- **Patients ask for it**
  - When given the option, many patients will choose pH probe testing if it will help avoid medication/empiric treatment
- **Proof of reflux/LPR in non-responders**
  - Also prove to patients that they do NOT have LPR
- **To determine severity of reflux**
  - Consideration for fundoplication
  - Treatment needs for patients with laryngeal cancer, stenosis or severe asthma
- **Symptom association for patients with challenging LPR-related diagnoses**
  - Chronic cough, globus, sinusitis, post-nasal drip
  - Proving that patients DON'T need PPI
- **It’s fun and interesting!**

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**BARIUM ESOPHAGRAM**

- Reflux testing options
  - Barium Esophagram/SS
    - Poor sensitivity
    - Decent specificity
    - Recent review:
      - 567 pts
      - Only 37% of pts with symptoms had detectable reflux on studies
      - Provocative moves raised this to 70%
      - Good assessment of motility in trained hands
      - Ability to assess mucosa

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**pH Probe Testing**

- Relatively invasive
- Controversy in device
  - Single probe, dual probe, NP probe, wireless probe
  - 24 – 48 hour snapshot
  - May not be predictable of a patient’s ‘normal’
- Controversy in interpretation
  - Evolving standard normal values for hypopharyngeal MII/pH
    - Does presence of acid imply LPR?
    - Does acid exposure cause symptoms?
    - Does the absence of acid rule out LPR?
  - Role of impedance-pH monitoring
  - Does a positive pH probe predict clinical response?
Reflux testing options

- Dx-pH – Restech
  - Upside:
    - Easy to place/tolerate
    - Can detect NP reflux(?)
    - Studies show improved scores w/fundoplication
  - Downside:
    - Normative data poor
    - Poor correlation of Dx-pH data with pH-MII
    - <17% of all Dx-pH events detected at lower esophageal pH sensors (!!!)
    - I don’t use it.

Multichannel Intraluminal Impedance with Dual pH

Dual pH-MII testing technique

Probe withdrawn to view electrodes
Probe delivered to bury upper impedance probe in PC segment
MCW Dual pH MII patient series

- 2010-2015
  - With Joel H. Blumin, MD FACS
  - 109 patients with symptoms suggestive of possible LPR (dysphonia, chronic cough, globus sensation, subglottic stenosis) were evaluated using a dual pH-MII system, as well as reflux finding score (RFS) and reflux symptom index (RSI) minimum symptom score
  - 1 pt could not tolerate, no SFX
  - 60 pts on PPI prior
    - Hold PPI 1 wk, H2 blockers 24 hrs before
  - pH cutoff 1 event, impedance 40 events

- Cumpston, EC, Blumin, JH, Bock, JM "Dual pH Multichannel Intraluminal Impedance Testing in the Management of Subjective Laryngopharyngeal Reflux Symptoms", In Review (Oto-HNS), presentation at Academy 2015 Dallas, TX

109 patients were evaluated with dual pH-MII studies between 2010-2015 with 51 (47%) studies interpreted as 'positive' for evidence of significant LPR, 43 (39%) were interpreted as 'negative', and 15 (14%) were 'equivocal'.

Primary indications for performing dual pH-MII probe studies included throat clearing/irritation (28%), cough (25%), chronic rhinosinusitis/post-nasal drip (24%), heartburn (17%), globus (15%), subglottic stenosis (11%), dysphonia (7%), and dysphagia (2%). Patients could list more than one symptom as a primary indication for the study.
MCW Dual pH MII patient series

Highest rates of positive study interpretation (63%) were noted for dysphonia, globus, and heartburn patients. Cough (52%), subglottic stenosis (50%), and chronic sinusitis (27%) patients had lower rates of positive study, while throat pain and dysphagia pts had no positive studies.

8/1/2016

• 2010-2015 study:
  - 8 patients went on to fundoplication, all had positive studies and on PPI prior to study
  - 13% of all positive studies
  - All of these patients had symptom improvement on follow-up exam
  - Current protocol in our clinic:
    - Nasal pepsin irrigation lavage
    - Pre-placement spit testing for pepsin
    - Spit collection 30 minutes after meals, bedtime, upon awakening
    - Concomitant 24-hr dual pH-MII ComforTEC LPR probe analysis
    - Comparing 20 patients to 20 controls (no LPR symptoms or history of reflux)
    - Expect study completion late 2017.
Conclusions

- Judicious use of empiric PPI with plan for endpoint, weaning
- Consider option of early objective testing for symptoms suggestive of LPR with MII-pH testing
  - Referral for fundoplication for positive patients
- Follow symptom-based algorithm for treatment
  - Videostroboscopy early in evaluation to detect subtle structural or neurologic issues
  - Speech therapy referral
  - Consider injection laryngoplasty
  - Gradated approach based on cost/benefit
  - Other testing modalities based on symptoms
Airway reflux significantly mediated by nonacid components for which typical GERD treatment does not suffice

- PPI therapy is the mainstay for treatment of GERD.
- Efficacy for the treatment of airway reflux, including LPR, remains doubtful.
  - Placebo-controlled trials failed to demonstrate any therapeutic benefit of PPIs (Ehner et al., 2003; Noordzij et al., 2001)
- MII-pH technology detects reflux events independent of pH of the refluxate.
  - Demonstrated inefficacy of acid-targeting therapeutics for LPR.
  - Association of symptoms with nonacid reflux (Tutuian et al., 2006).
  - Symptom alleviation upon surgical intervention that abrogate reflux of all gastric contents (Iqbal et al., 2009)
Pepsin may contribute to symptoms and endoscopic findings associated with nonacid LPR and despite PPI therapy

- Studies analyzing cell morphology (EM), mitochondrial function (MTT assay), and expression of stress response genes (RT-PCR) in laryngeal specimens and cultured hypopharyngeal epithelial cells treated with pepsin confirmed that endocytosed pepsin causes toxicity (Johnston et al., 2009; 2010).

- Nonacid pepsin induces a pro-inflammatory cytokine gene expression profile in hypopharyngeal cells similar to that in reflux esophagitis and which are known to contribute to the pathophysiology of GERD (Samuels et al., 2009).

Anti-pepsin therapeutic for reflux disease

- $26 billion/year spent on PPIs for LPR (Francis et al., 2013)
  - Despite their poor efficacy

- Novel therapeutic that targets pepsin (Bardhan et al., 2012)
  - Irreversible inhibitors of peptic activity
  - Receptor antagonists

Developed and optimized high through-put screening assays

- Assay 1: Binding assay with fluorescently labeled pepstatin
- Assay 2: Enzymatic assay with a labeled protein substrate (fluorescent casein)
**Developed and optimized high through-put screening assays**

**Assay 1:** Binding assay with labeled pepstatin

- Fluorescent pepstatin + Inhibitor → Low signal
- Fluorescent pepstatin + Labeled pepstatin → High signal

**Assay 2:** Enzymatic assay with a labeled protein substrate (fluorescent casein)

- Labeled casein + Pepsin → Low signal
- Fluorescent pepstatin + Labeled casein → High signal

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**Screened libraries of pharmacologically active compounds**

Binding assay (labeled pepstatin)

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Gino Scuncio, BS; Tina Samuels, MS; Chris Goetz, BS; Alex Dzubinski, BS
Ongoing studies

- Co-crystallization studies of pepsin with hit compounds identified through screening assays
  Nicholas Chiang, PhD
  UCI Microbiology

- Developing analogs of known hit compounds
  Simone Lucarini, PhD
  University of Urbino, Italy

In vivo mouse model to test lead compounds

- Does pepsin cause mucosal inflammation in vivo?
  Pepsin (0.3mg/ml, pH7) or vehicle control, 5 installations in esophagus and laryngopharynx at one week intervals

- Does pepsin promote carcinogenesis in vivo?
  Pepsin +/- MNU, 5 installations in esophagus and laryngopharynx at one week intervals, euthanized at 20 weeks

Test lead compounds

Esophageal adenocarcinoma (EAC) disease statistics

Incidence has risen 600% since 1970s

50% never selected for screening

5 year survival: 17%
Local synthesis of pepsinogen in Barrett’s esophagus – role in progression to esophageal adenocarcinoma

- Presence of chief cells and pepsinogen mRNA and protein in BE (Pols et al., 1988; Mangla et al., 1985; Kahrilas, 2004; Antoniolo, 2004)
- Absence of pepsin and pepsinogen in normal esophagus (Johnston et al., 2006)
- Historically concluded that local synthesis in BE did not pose a significant risk
- BUT... nonacid pepsin now known to cause mucosal inflammation and to promote laryngeal carcinogenesis (Kiely et al., 2014; Samuels et al., 2009)

Jon Gould, MD
MCW
Pepsin (0.1mg/ml, pH7) causes a time-response increase in cytotoxicity / mitochondrial damage in esophageal epithelial cells

\[ y = -0.0016x + 0.1751 \]

Mean Absorbance

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Markers of Barrett's esophagus (van Baal et al., 2008)

- KRT 10 expressed in normal esophagus only
- Dose response decrease in KRT 10 following exposure to pepsin (pH7, 4 wks) p<0.009
- KRT 8 marker of BE
  - Increased KRT 8 following exposure to pepsin (pH7, 4 weeks) p<0.02
- CDX2 expressed in BE, not normal esophagus
  - Performing IF after chronic pepsin treatment

Effect of pepsin on IL-8 protein expression in esophageal Het-1A cells

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Local synthesis of H/K ATPase (proton pumps) in Barrett’s esophagus and esophageal adenocarcinoma

In vivo mouse models

- Mouse model with Frank Ondrey, MD
- Pepsin +/- MNU
- Transgenic mouse model with Michele Battle, PhD
  - Tet-ON approach to generate transgenic mice expressing pepsinogen and proton pumps in the esophagus in response to doxycycline
Case Presentation

9 year old female with several month history of cough.

- History: Present all the time, worse at night, dry in nature. History of colds, but no antibiotics. No frequent burping, dysphagia, chest discomfort.
- PMH: Asthma, treated for GERD as an infant

Case Presentation

- Exam:
  - Intermittent dry cough
  - Boggy turbinates, otherwise normal
- Flexible scope:
  - Decongests well, clear secretions
  - Adenoids mildly hypertrophied
  - Cobblestoning of posterior pharyngeal wall
  - Normal vocal fold mobility
  - Mild edema and erythema of post-cricoid
Audience response

What is your next step in management?

A. Refer to asthma/allergy
B. Antibiotic therapy
C. GERD precautions
D. H2 blocker
E. PPI

Risk for GERD

- Preterm infants
- Children with neurologic impairment
- Repaired esophageal atresia or achalasia
- Hiatal hernia
- Lung transplantation
- Chronic respiratory disorders
- Obesity


Testing

- Gold standard: Multichannel intraluminal impedance with pH monitoring (MII-pH); documents both acid and non-acid reflux.
- Most common: 24-h dual probe pH monitoring.
- Barium esophagram preferred in < 1 year of age for detecting associated anatomical anomalies.
- Scintigraphy.
- Flexible scope for LPR associated diseases (nodules, RRP, LM, granulomas); remains controversial for suspected laryngopharyngeal reflux.


Audience response

What is your preferred method to treat GERD in children?

A. H2 blocker
B. PPI
C. Conservative measures
D. Refer to GI

Your poll will show here

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2. Make sure you are in Slide Show mode

Still not working? Get help at polliv.com/app/help
Or Open poll in your web browser
What is the evidence?

- 20 children with coughing spells while being monitored with a pH probe.
  - 90% of coughs did not correspond with a reflux event.
  - Chronic irritation of laryngeal tissues from reflux is the predominant culprit.

- Asthma
  - Children with chronic cough underwent EGD; 75% with positive biopsies also had a history of asthma.
  - 40 children with cough for > 8 weeks; reflux and asthma were present in nearly half the patients and another quarter of the patients had multiple causes.

- Evaluation of chronic cough - multiple factors may be playing a role.

LPR treatment in children

- Less than 10% of patients are tested for GERD prior to starting Rx.
- ~33% of infants are given PPI as first line.
- Data do not support using GERD-related agents to treat nonspecific cough in children.

Laryngomalacia and GERD

- Systematic review (Hartl) 37 Studies, 1295 infants with laryngomalacia (LM) and acid reflux (GERD).
  - Levels of evidence level 2a (n = 1) to 4 (n = 23).
  - Reflux prevalence 59% (OR = 1.15)
  - Dual-probe pH monitoring with increased prevalence of reflux in severe vs. mild LM (OR = 9.86)
  - LM symptoms and histologic improvement with GERD therapy

- LM and GERD coexist; unclear if GERD is causative for LM
H2 blocker in children

• For mild or intermittent symptoms of GERD.
• Rapid onset of action; well suited for providing symptomatic relief.
• Less effective than PPIs, especially for chronic use.
• Increased risk of enteric infection, particularly C. difficile and community-acquired pneumonia


PPI risks

• Increased risk of enteric infection, particularly C. difficile and community-acquired pneumonia
• Small intestinal bacterial overgrowth occurs with long-term PPI use

Tomo et al. Abdomen Pan 2010;37:756-766
Sarin et al. 2011;116:53-58
Lombrano et al. CMA J Gastroenterol 2010;6:323-326

Conservative measures

• Dietary modification
  – Weight loss
  – Food avoidance: caffeine, tomato, spicy, citrus, deep fried, fatty foods, chocolate
  – No food/meal < 1 hour prior to sleep
  – Smaller, more frequent meals

Tsuy J Curr Treat Options Gastroenterol 2007;10:391-403
Conservative measures

• Position changes
  – Raising the head of the bed
  – Left lateral decubitus sleeping position

• Avoidance of second hand tobacco smoke

Keltenbach et al. Arch Intern Med 2006;166:955-71
Tipnis et al. Curr Treat Options Gastroenterol 2001;10:391-400

Thank you