LPRD?

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Laryngopharyngeal Reflux

- Between 1990 and 2001
  - Reflux related visits to ENT practices increased >300%
  - Prescriptions for PPIs increased 14-fold
- Today in ENT practices
  - Patients present daily with hoarseness, dysphagia, globus, throat clearing, and/or cough => Laryngoscopy => tentative LPR diagnosis => PPI therapy for 2-3 months and lifestyle modifications => about half return with persistent symptoms
- Is this approach working? Could we achieve better, more consistent results?
Challenges of LPR

- Pathophysiology
  - Not fully understood
  - Several new mechanisms proposed within the last few years

- Diagnosis
  - Numerous, widely ranging symptoms
  - Confused with other disorders
  - Co-existence with other disorders
  - Poor sensitivity and specificity of even “gold standard” tests

- Treatment
  - No definite standard (wide variety of approaches)
  - Conflicting evidence
  - High failure rate of even the most accepted treatments
Traditional mechanism

- Retrograde flow of gastric acid and pepsin leading to laryngeal mucosal damage and impaired mucociliary clearance
  - Up to 50 reflux events per day is normal and tolerated in the distal esophagus
  - As few as 3 reflux events per week touching the larynx can injure vocal fold mucosa

Barriers to reflux

- Lower esophageal sphincter (most important)
- Upper esophageal sphincter
- Esophageal peristalsis
- Gastric emptying
Emerging alternate/complimentary mechanisms

- Role of pepsin in non-acidic reflux
  - Johnston et al 2010
  - Post-cricoid epithelial cells contained pepsin in patients with symptoms of LPR while those of controls did not
  - Inactivated pepsin at pH 7 is taken into cells by receptor-mediated endocytosis and reactivated, leading to mitochondrial and overall cell damage
  - Cell damage was prevented by irreversible inactivation of pepsin prior to cell exposure or blockage of pepsin uptake
Emerging alternate/complimentary mechanisms
- Heterotropic gastric mucosal patch (aka cervical inlet patch)
  - Ectopic gastric mucosa, typically located between the UES and LES
  - Congenital
  - Chong and Jalihal 2010
  - 26 (5.6%) of 462 consecutive patients undergoing upper endoscopy during an 18 month period had a patch
  - 73.1% of patients with a patch experienced LPR symptoms (chronic cough, hoarseness, globus) vs. 25.9% of patients without a patch
  - However, in most of the patients with a patch, the symptoms were mild; only 3 of the 26 had been referred for LPR symptoms
Diagnosis
The most common symptoms of LPR

- Hoarseness/dysphonia
- Globus sensation
- Chronic throat clearing
- Vocal fatigue
- Voice breaks
- Sore throat

From Aviv and Collins. Upper Aerodigestive Manifestations of GERD. Cummings Otolaryngology Head and Neck Surgery. Listed in order of frequency, pooled from several studies
The next most common symptoms of LPR

- Neck pain
- Excessive throat mucus
- Chronic cough
- Dysphagia
- Odynophagia
- Postnasal drip
The lesser most common symptoms of LPR

- Halitosis
- Otalgia
- Laryngospasm
- Asthma exacerbation
- Loss of upper singing range
- Prolonged warmup time in singers
- Heartburn/regurgitation
Reflux Symptoms Index (RSI)

Within the past month, how did the following problems affect you? Rank them from 0 (no problem) to 5 (severe problem).

1. Hoarseness or a problem with your voice
2. Clearing your throat
3. Excess throat mucus or postnasal drip
4. Difficulty swallowing food, liquids, or pills
5. Coughing after you have eaten or after lying down
6. Breathing difficulties or choking episodes
7. Troublesome or annoying cough
8. Sensations of something sticking in your throat or a lump in your throat
9. Heartburn, chest pain, indigestion, or stomach acid coming up

Endoscopic Exam

- Laryngoscopy
  - Fiberoptic
  - Rigid

- Videostroboscopy
  - Changed or modified the diagnosis in 10-47% of adult dysphonic patients with no laryngeal anatomic abnormalities
  - Critical for diagnosis in 27-68% of cases
Reflux Finding Score

- Pseudosulcus: 0, absent; 2, present
- Ventricular obliteration: 0, none; 2, partial; 4, complete
- Erythema/hyperemia: 0, none; 2, arytenoids only; 4, diffuse
- Vocal fold edema: 0, none; 1, mild; 2, moderate; 3, severe; 4, polypoid
- Diffuse laryngeal edema: 0, none; 1, mild; 2, moderate; 3, severe; 4, obstructing
- Posterior commissure hypertrophy: 0, none; 1, mild; 2, moderate; 3, severe; 4, obstructing
- Granuloma/granulation: 0, absent; 2, present
- Thick endolaryngeal mucus: 0, absent; 2, present

24-hour pH monitoring

- Dual pH probe (esophageal and hypopharyngeal) was considered the “gold standard” for the diagnosis of LPR until recently
  - Poor sensitivity (75-80%)
  - False negative rate up to 50%
  - Poor predictor of response to PPI therapy

- Combined multichannel intraluminal impedance and pH (MII/pH) monitoring
  - Newer, preferred technique
  - Can distinguish between liquid, gas, or mixed reflux events
  - Detection of acid and nonacid reflux
  - Improved diagnostic yield
24-hour pH monitoring

- Restech oropharyngeal probe
  - Minimally invasive, well-tolerated
  - Unlike standard pH probe
    - Liquid immersion not required
    - Detects aerosol
  - Good correlation with hypopharyngeal pH probe for measuring duration of acid exposure (Golub et al, 2009)
  - Cannot detect non-acidic reflux events
Controversies in the diagnosis of LPR

- Non-specific nature of symptoms—misdiagnosis
- Coexistence of other disorders with LPR leaving patients symptomatic even if LPR is treated
- Non-specific nature of laryngoscopy findings—misdiagnosis
  - High inter-rater variability
- Questionable value of pH monitoring
- Overall lack of a definitive, highly sensitive and specific gold standard test
264 new patients referred to the Vanderbilt Voice Center with a primary complaint of hoarseness

148 patients had taken a PPI in 2 months prior to initial evaluation, Group 1 (30%) had stopped the PPI due to continued hoarseness and Group 2 (70%) had continued the PPI but had persistent hoarseness and other throat complaints

_Laryngoscope_
Final diagnoses

- GERD or LPRD (38%)
- Muscle tension dysphonia (MTD) (30%)
- Vocal fold lesion (30%)
- Vocal fold paralysis (10%)
- Vocal fold cancer (2%)

Voice therapy most common therapy for both groups (35% combined) with an improvement in 63%
Cohen and Garrett (2008)

- 116 patients had not taken a PPI
  - 14.6% were started on a PPI
    - 50% had improvement
  - 85.4% were treated with voice therapy
    - 78.6% had improvement
On the subject of MTD:
- Occurs in 20 to 40% of patients with voice complaints
- Can frequently coexist with LPR
- Symptoms include hoarseness, reduced vocal stamina, increased effort to talk, pain with phonation, and excessive throat phlegm
Thomas and Zubiaur (2013)

- Chart review of 105 patients with voice-related disorders referred to a single practice with a previous diagnosis of LPR over a 3 year period

- 82 (78%) were on PPIs; 23 (22%) were on a non-specified anti-acid treatment

- 5% reported they had significant improvement in hoarseness after prior treatment; 13% had mild improvement; 79% had no improvement; 3% had worsening symptoms

*Eur Arch Otorhinolaryngol (Private clinic in Portland, OR)*
Final diagnoses for the patients were diverse, but none of the patients were diagnosed with persistent LPR.

Most common single diagnosis was MTD—29 (28%) of patients.

After various treatments as indicated, 61% of patients had improvement, 6% had no change, 22% were lost to follow up, and 3% refused advised treatment.

*Eur Arch Otorhinolaryngol (Private clinic in Portland, OR)*
“Pathophysiology and treatment of muscle tension dysphonia: a review of the current knowledge”

Review of the MEDLINE and CENTRAL literature on MTD from 1950 through 2009

MTD definition:
- The pathological condition in which an excessive tension of the (para)laryngeal musculature, caused by a diverse number of etiological factors, leads to a disturbed voice

*Journal of Voice*
Van Houtte et al (2011)

- **Primary MTD:**
  - Dysphonia in the absence of concurrent organic vocal fold pathology
  - Excessive, atypical, or abnormal laryngeal movements during phonation, without obvious psychogenic or neurologic etiology
  - Occurs primarily in women
  - 10-40% of caseloads at a voice center

- **Secondary MTD**
  - Dysphonia in the presence of an underlying organic condition

*Journal of Voice*
Key features of MTD diagnosis

- History of vocal misuse/abuse, stressful situations
- Visible and palpable tension around the larynx
- Tightness of the paralaryngeal musculature, laryngeal rise, decreased thyrohyoid space, and focal tenderness
Van Houtte et al (2011)

- Laryngoscopy/stroboscopy findings:
  - MTD 1—laryngeal isometric contraction with posterior open chink because of a hypertonic state of the posterior cricoarytenoid muscle
  - MTD 2—supraglottic contraction in which the ventricular folds are adducted to the midline
  - MTD 3—anterior-posterior contraction that results in a reduced space between the epiglottis and arytenoids
  - MTD 4—extreme anterior-posterior contraction or squeeze
Van Houtte et al (2011)

- **Treatment**
  - Patient education and vocal hygiene
  - Voice therapy
    - Breaks the cycle of decompensation and overcompensation of the voice
  - Circumlaryngeal manual therapy (CMT)
    - Applying pressure and massage to sites of focal tenderness and nodularity in the hyoid-laryngeal musculature while the patient hums or sustains vowels
  - If no improvement within the first two sessions, unlikely to be of benefit
  - Medical and surgical management of organic disorders as appropriate
15 consecutive patients with a primary voice disorder or presenting complaint of a lump in the throat
- Excluded if on medication for reflux or allergy

- RSI, RFS, SPT, and nasal nitric oxide (NO) levels measured in all patients
  - LPR diagnosed if RSI >13 and RFS >10
  - Allergy diagnosed if both SPT positive and NO level elevated
Randhawa et al (2010)

Results

- 10 (67%) patients diagnosed with allergy
- 3 (20%) diagnosed with LPR (all also tested positive for allergy, included in the 10)
- 5 (33%) of patients were negative on all tests
“Rhinogenic laryngitis, cough, and the unified airway” (review)

Chronic rhinogenic laryngitis

- Defined as inflammation of the larynx resulting in related signs and symptoms that last for at least 2 weeks
- Symptoms: hoarseness, throat clearing, straining, globus, odynophagia, cough; often with a co-seasonal variation
- Pharyngeal dryness and post-nasal drainage can lead to mucosal irritation of the larynx and pharynx => itching/tickling in the throat => throat clearing and coughing
- Laryngeal exam: increased, thick mucus in the endolarynx that can bridge the vocal folds, mild vocal fold edema, mild to moderate erythema of the arytenoid mucosa
Inhalant antigen or irritant exposure, Sinusitis

- Nasal congestion
- Runny nose
- Postnasal Drainage
- Pharyngitis/Laryngitis
  - Throat Clearing
  - Coughing
  - Vocal fold edema
  - Dysphonia
- Upstream mucous migration

Pulmonary congestion
Bronchospasm, coughing
Inhalational challenge studies

Authors of the review and colleagues at Wayne State

Patients with documented allergy to the house dust mite *Dermatophagoides* underwent direct inhalational challenge of the larynx with aerosolized antigen in increasing concentrations.

With increasing antigen exposure, patients developed:
- Coughing
- Throat clearing
- Dyspnea
- Increased mucus in the larynx on endoscopy
Krouse and Altman (2010)

Management
Controversies in the management of LPR

- Highly variable response to PPIs
- Paucity of high quality, randomized, placebo-controlled trials
- Many small trials show strong placebo effect and no significant difference in treatment outcomes between PPI and placebo
- High variation in treatment regimens
  - Starting dose and length of treatment
  - When to escalate/deescalate
  - H2 blockers
- Question of correct diagnosis
Cohen et al (2012)

- Cross-sectional survey of 1,000 general otolaryngologists to investigate treatment approaches for adult dysphonic patients without obvious laryngeal anatomic abnormalities
- 27% response rate
Table 1. Treatment Approach to the Adult Dysphonic Patient with Normal Vocal Fold Mobility and No Vocal Fold Lesions on Laryngoscopy

<table>
<thead>
<tr>
<th>Next Management Steps</th>
<th>Percentage^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refer to speech pathology</td>
<td>63.0</td>
</tr>
<tr>
<td>Prescribe proton pump inhibitor</td>
<td>58.6</td>
</tr>
<tr>
<td>Obtain stroboscopy</td>
<td>57.9</td>
</tr>
<tr>
<td>Refer to laryngologist</td>
<td>11.7</td>
</tr>
<tr>
<td>Prescribe oral steroid</td>
<td>9.2</td>
</tr>
<tr>
<td>Obtain reflux testing</td>
<td>5.1</td>
</tr>
<tr>
<td>Refer to neurologist</td>
<td>1.1</td>
</tr>
<tr>
<td>Obtain computed tomography/magnetic resonance imaging</td>
<td>0.4</td>
</tr>
<tr>
<td>Obtain laryngeal electromyography</td>
<td>0.4</td>
</tr>
</tbody>
</table>

^aRespondents may have more than 1 response.
### Table 5. Methods for Testing/Determining If Adult Dysphonic Patient Has Reflux

| Method                              | Percentage
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Daily proton pump inhibitor (PPI)</td>
<td>60.8</td>
</tr>
<tr>
<td>Laryngeal findings</td>
<td>58.9</td>
</tr>
<tr>
<td>Associated throat symptoms</td>
<td>42.4</td>
</tr>
<tr>
<td>Twice daily PPI for 1 to 2 mo</td>
<td>39.9</td>
</tr>
<tr>
<td>Refer to gastroenterology</td>
<td>22.3</td>
</tr>
<tr>
<td>pH probe study</td>
<td>17.9</td>
</tr>
<tr>
<td>pH/impedance study</td>
<td>15.8</td>
</tr>
<tr>
<td>Daily PPI for 3 to 4 mo</td>
<td>10.9</td>
</tr>
<tr>
<td>Twice-daily PPI for 3 to 4 mo</td>
<td>9.5</td>
</tr>
<tr>
<td>Empiric H₂ blocker</td>
<td>8.4</td>
</tr>
<tr>
<td>Bravo capsule</td>
<td>3.2</td>
</tr>
<tr>
<td>Restech pH catheter</td>
<td>1.5</td>
</tr>
<tr>
<td>Transnasal esophagoscopy</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*R Respondents may have more than 1 response.
Table 6. Next Step in Management for Adult Dysphonic Patient Who Failed Initial Treatment

<table>
<thead>
<tr>
<th>Next Management Step</th>
<th>Percentagea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voice therapy</td>
<td>58.2</td>
</tr>
<tr>
<td>Obtain stroboscopy</td>
<td>46.9</td>
</tr>
<tr>
<td>Refer to gastroenterology</td>
<td>43.8</td>
</tr>
<tr>
<td>Extend or increase proton pump inhibitor</td>
<td>33.3</td>
</tr>
<tr>
<td>Allergy evaluation</td>
<td>31.9</td>
</tr>
<tr>
<td>Refer to laryngologist</td>
<td>30.8</td>
</tr>
<tr>
<td>Reflux testing</td>
<td>25.6</td>
</tr>
<tr>
<td>Oral steroid trial</td>
<td>7.3</td>
</tr>
<tr>
<td>Obtain computed tomography/magnetic resonance imaging</td>
<td>5.1</td>
</tr>
<tr>
<td>Refer to neurology</td>
<td>3.6</td>
</tr>
<tr>
<td>Refer to pulmonary</td>
<td>2.6</td>
</tr>
<tr>
<td>Laryngeal electromyography</td>
<td>1.8</td>
</tr>
<tr>
<td>Refer to rheumatology</td>
<td>1.1</td>
</tr>
<tr>
<td>Antibiotic trial</td>
<td>0.7</td>
</tr>
</tbody>
</table>

aRespondents selected the top 3 responses.
Objective was to assess the effectiveness of anti-reflux therapy for patients with hoarseness. Evaluated all randomized and quasi-randomized, controlled, double-blinded trials to that date.

Primary measures:
- Proportion of patients with complete and partial resolution of hoarseness
- Quality of life measures
- Disease-specific measures
A total of 302 studies of hoarseness were identified

Only 6 randomized controlled trials were identified, all comparing gastric acid suppression with PPI vs placebo; however, none met selection criteria, so no analysis could be performed.

4 of the 6 studies showed no significant difference between the treatment and placebo arms, and a strong placebo effect was found across all 6 studies.

- Prospective, randomized, double-blind, placebo-controlled trial

- Esomeprazole (Nexium) 20 mg BID vs placebo

- 62 patients with an RSI > 13 and RFS >7 were enrolled, 58 completed the study

- RSI and RFS measured at baseline, 6 weeks, and 3 months

- At 6 weeks, the only significant difference in the groups was a decrease in heartburn in the esomeprazole group (P <0.05)
At 3 months

- Statistically significant decrease from baseline RSI in both treatment and control groups (P <0.001), with a statistically significant greater decrease from baseline in the treatment group (P<0.05)
- Statistically significant greater decrease in RFS in the treatment group
  - Greatest difference in posterior commissure hypertrophy, followed by erythema and diffuse laryngeal edema
  - In the control group, no significant decrease in laryngeal erythema or ventricular obliteration from baseline
- 78% of patients in the esomeprazole group felt they had complete resolution of symptoms vs 42% in the placebo group (P=0.006)
Prospective, randomized, double-blind, placebo-controlled trial

Rabeprazole (Aciphex) 20 mg BID vs placebo for 12 weeks

86 patients with LPR symptoms and RFS >7; 82 completed the study
  Excluded patients with allergic causes of laryngitis

All patients were educated on lifestyle modifications

RSI and stroboscopy (with RFS) performed at baseline, 6 weeks, 12 weeks, and 18 weeks (6 weeks after discontinuation of treatment)
Lam et al (2010)

- **RSI**
  - Significantly reduced at 6 weeks and 12 weeks in the treatment group compared to control
  - No significant difference between groups at 18 weeks

- **RFS**
  - No statistically significant difference between groups at 6, 12, or 18 weeks; however, significance was defined at the 0.01 level (due to multiple comparisons in the study, to reduce risk of type I error), and the difference in RFS at week 12 was 0.54 ±0.69; P = 0.017

- Results suggest a longer duration of PPI therapy may be necessary
Concurrent nonrandomized comparative trial investigating effectiveness of combined voice and medical therapy for LPR vs. medical therapy alone

100 patients with LPR (RSI >13 and RFS >7) split into two groups of 50

Study group
- Voice therapy (30 min sessions once weekly x 3 months)
- Omeprazole 20 mg BID for 3 months

Control group
- Omeprazole 20 mg BID for 3 months

All subjects evaluated by RSI, RFS, voice handicap index (VHI), and perceptual voice analysis (GRBAS scale) at 1, 2, and 3 months
RSI significant changes (≥5)
- Study group: 42% (1 month), 66% (2 months), 68% (3 months)
- Control grp: 6% (1 month), 16% (2 months), 46% (3 months)

RFS significant changes (≥3)
- Study group: 2% (1 month), 4% (2 months), 50% (3 months)
- Control grp: 0% (1 month), 8% (2 months), 18% (3 months)

VHI significant changes (≥15)
- Study group: 36% (1 month), 40% (2 months), 48% (3 months)
- Control grp: 2% (1 month), 4% (2 months), 20% (3 months)
GRBAS significant changes ($\geq 1$)
- Study group: 50% (1 month), 64% (2 months), 72% (3 months)
- Control grp: 6% (1 month), 20% (2 months), 38% (3 months)

Conclusions
- Medical therapy (PPI) reduces chemical irritation
- Voice therapy promotes recovery by blocking causes of mechanical irritation
Fackler et al (2002)

- 16 patients with GERD confirmed by pH monitoring and 18 healthy controls
- Omeprazole 20 mg BID x 2 weeks, then ranitidine 300 mg added at bedtime for 4 weeks
- Acid production was suppressed further on day 1 but returned to baseline PPI level by 1 month due to tolerance
- Recommended use on as-needed basis rather than daily therapy
Enhanced Approach to the Patient
When LPR is considered

Key History Points
- Is heartburn or reflux present?
- Does the patient have symptoms more consistent with allergy?
  - Personal or family history of allergic rhinitis or asthma
  - Throat dryness or itching
  - Co-seasonal variation in symptom severity
- Post-nasal drip—can be symptom or cause
- Does the patient have symptoms more consistent with MTD?
  - Vocal strain
  - Vocal abuse/misuse (singers, teachers, preachers, lawyers)
  - Tension or pain involving the paralaryngeal musculature

*GERD symptoms not requisite for LPR, but PPI response improved if they are*
When LPR is considered

- **Key Examination Findings**
  - Nasal signs of allergy or chronic sinusitis
  - Cobblestoning of the posterior pharyngeal wall
  - Tension or pain on palpation of the paralaryngeal musculature
  - Decreased thyrohyoid space/laryngeal elevation with phonation
  - **Laryngoscopy**
    - Thick endolaryngeal mucus bridging the vocal folds suggests a diagnosis of allergy over LPR
If LPR is the presumed diagnosis

- **Initial treatment**
  - Lifestyle modifications
    - Tobacco cessation and weight loss
    - Head of bed elevation
    - No food intake at least 3 hours prior to recumbence
  - Food avoidances
  - 3 month trial of PPI BID 30 minutes prior to morning and evening meals
  - Strongly consider voice therapy for 3 months
If LPR is the presumed diagnosis

- If initial therapy is successful
  - Taper PPI
  - If symptoms recur, increase PPI
  - Some may require daily PPI indefinitely; may consider surgery

- If initial therapy fails
  - Reassess history for alternate diagnoses
  - Perform or refer the patient for videostroboscopy

- If diagnosis remains uncertain
  - 24-hour MII/pH probe or Restech probe
  - Allergy testing
  - Perform or refer for upper endoscopy (TNE, EGD)

- If diagnosis is confirmed as reflux but current medical therapy fails
  - Consider referral for surgical evaluation (fundoplication)
Take Away Points

- LPR is a real disease affecting many voice patients, but it is likely over-diagnosed in clinical practice.
- Strong consideration should be given to alternate diagnoses in the workup of LPR, especially muscle tension dysphonia and allergy.
- Voice therapy improves the speed and likelihood of resolution of LPR symptoms.
- Videostroboscopy is essential for patients diagnosed with LPR who fail initial therapy.
References