Introduction:

Extraesophageal reflux disease has become a hot topic in the realm of otolaryngology within the last 15 years. Many otolaryngologic clinic visits deal with the proposed symptoms of extra-esophageal reflux. Twenty-five percent of adults experience reflux on a monthly basis and 5-10% of patients experience reflux on a daily basis. Proton pump inhibitors (PPI’s) are now the 3rd most commonly prescribed medication class in the market speaking to the increased awareness of the disease process. Therefore it is important that we recognize how and when to treat patients appropriately for their symptoms, but also recognize when to refer patients for further workup to rule out more severe causes of symptoms.

Background:

In 2006 the Montreal Consensus went on to define GERD as:

"a condition that develops when the reflux of the stomach contents causes Troublesome symptoms and/or complications”

They went on to define Troublesome as:

“adversely affecting an individual’s well-being”

The biggest concern with regards to esophageal reflux is metaplasia of the esophageal nonkeratinizing squamous mucosa to a more glandular lining called Barrett’s Esophagus. Patients that develop Barrett’s esophagus are at significantly higher risk for developing adenocarcinoma of the esophagus and therefore are monitored closely for signs of disease. Despite these effects, the Montreal Consensus also went on to describe extra-esophageal syndromes associated with reflux including reflux cough, reflux laryngitis, and reflux asthma. These will be the topic of our discussion today.
Relevant Anatomy and Physiology:

The esophagus is an 18 to 22cm tubular structure in the neck and chest that connects the pharynx to the stomach. It is critical for the coordinated effort of swallowing. The upper 1/3 consists of striated muscle, the inferior 1/3 consists of smooth muscle and the middle 1/3 is a blend of the two. Again the mucosa of the esophagus is nonkeratinizing stratified squamous epithelium throughout its length. The upper esophageal sphincter has an inner circular layer that is associated with the cricopharyngeus and the lower esophageal sphincter opens with peristalsis. It has a resting tone of 15-45mm Hg.

Acid from the stomach is produced in the parietal cell. Acetylcholine, gastrin and histamine all induce acid production utilizing the proton pump. As acid in the form of hydrogen ions are pumped into the lumen of the stomach, chloride ions follow while potassium ions are pumped out of the lumen. This results in a net decrease in pH of the stomach. Antihistamines such as ranitidine work at the histamine receptor to competitively inhibit acid production, but proton pump inhibitors such as omeprazole work at the pump itself to significantly decrease acid production, irrespective of hormonal activity. As such gastrin will rise to significantly high levels in patient using PPI’s. Ultimately acid build up in the stomach can enter the esophagus, pharynx, and larynx as a result of lower esophageal sphincter dysfunction. This ultimately causes symptoms and signs associated with GERD.

Empiric Therapy

In most otolaryngology and general medicine clinics, patients often report with a myriad of symptoms ranging from heartburn, belching, and regurgitation to sore throat, voice changes and cough. Below is a table outlining the different symptoms associated with both GERD and Laryngopharyngeal reflux disease (LPRD).

<table>
<thead>
<tr>
<th>GERD</th>
<th>LPRD</th>
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<tr>
<td>Heartburn</td>
<td>Dysphagia</td>
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<tr>
<td>Epigastric pain</td>
<td>Sore throat</td>
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<tr>
<td>Shortness of breath</td>
<td>Halitosis</td>
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<td>Regurgitation</td>
<td>Voice changes</td>
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<tr>
<td>Belching</td>
<td>Cough</td>
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<tr>
<td>Chest pain</td>
<td>Throat clearing</td>
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<td></td>
<td>Globus sensation</td>
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Empiric therapy has often been the primary treatment for patients with these complaints. A Cochran review from 2006 by van Pixteren et al, looked at PPI versus H2-blockers versus prokinetic medications in the treatment of Reflux. They found that 19 studies showed significantly improved reflux symptom improvement after empiric therapy with PPI’s compared to the other medications and this fact stayed significant even for patients with endoscopic negative reflux disease. It was therefore their conclusion that empiric therapy with PPI’s were effective and superior to other medications in improving symptoms associated with reflux.
As outlined above though, reflux is in general, a problem with the lower esophageal sphincter and not acid production. This begs the question, “Should we be treating so many patients with PPI’s if that is not truly fixing the problem?” Several studies have looked at this question. Yu et al. looked at PPI or H2 blocker therapy and their risk associated with pathologic fractures. They performed a meta-analysis on 10 papers addressing this issue and essentially found that there was a modest increase in the relative risk of pathologic hip fractures for both men and women taking PPI’s. This was not true for H2-blockers. None of the papers evaluated were RCT’s and most were case control and prospective observational studies, however the concern is still there.

Others have discussed concerns with regard to the use of PPI’s and Plavix. Bhatt et al. performed a double blinded, placebo controlled, randomized controlled trial of 7600 patients receiving Plavix plus either PPI or placebo. They showed that there were no significantly increased events in either group including both GI bleeds and cardiovascular events. Interestingly they also performed a subgroup analysis in patient who recently received a stent and were at the highest risk for a cardiovascular event, and still there were no significant differences in groups. Although this study is negative there is still concern about the concurrent use of these medications.

Finally, a study performed by Reimer et al. in 2009 looked at the dependence of PPI therapy that patients develop. In another randomized, double blinded, placebo controlled trial, 12 patients received either 12 weeks of placebo or 8 weeks of esomeprazole 40mg/day followed by 4 weeks of placebo. The GI Symptom Rating Score (GSRS) was evaluated at baseline and on weeks 9, 10, 11 and 12. Both groups had similar scores at baseline however patients treated with therapy that were withdrawn during weeks 9-12 experience a significantly higher GSRS compared to placebo showing that dependence does occur. Therefore it is important to be judicious with regards to empiric therapy haphazardly in all patients.

Extra-esophageal Syndromes:

At this point it is time to discuss the specific syndromes for which we are commonly asked to evaluate patients based on their extra-esophageal symptoms. We will focus on the three most commons symptoms including asthma, chronic cough, and laryngopharyngeal reflux disease.

Asthma

Patients with asthma and reflux undergo a vicious cycle with regards to tracheobronchial effects of the disease. It starts with direct injury of the mucosa by acid that leads to an asthma exacerbation, increased cough, and ultimately increased negative intra-thoracic pressure, which again increased reflux patterns and additional injury. Additionally treatment associated with asthma including steroids and beta agonists can lower the tone of the lower esophageal sphincter, thus increasing the risk of reflux into the airway.

Leggett et al. performed a study looking at dual probe pH monitoring in 52 patients with difficult to control asthma. Seventy-five percent of patients had evidence of reflux with 55%
being above the lower esophageal sphincter and 34.6% at the proximal probe. Only 16% of coughing episodes, however were associated with a reflux event documented by the patients. Therefore this study argued that although patients may have concurrent reflux, it does not likely play a role in making asthma worse.

The American Lung Association (ALA) Asthma Clinical Research Center performed a double blinded, placebo controlled, randomized controlled trial of 412 patients with uncontrolled asthma but no reflux symptoms. They placed these patients on esomeprazole 40mg BID versus placebo for 24 weeks and performed ambulatory 24 hour pH monitoring at baseline. 40% of the patients were found to have asymptomatic reflux at baseline based on pH probe criteria, however no significant difference in asthma exacerbations or PFT testing were found in the treatment group.

In contrast to the ALA trial, Kiljander performed a similar double blinded, placebo controlled, randomized controlled trial of 770 patients with moderate to severe asthma. Patients were randomized to placebo or esomeprazole 40mg BID for 16 weeks. Patients in the treatment group showed significant improvements in PFT’s especially in patients who had pretreatment nocturnal symptoms and reflux.

Therefore, based on these studies my recommendations would be that empiric treatment for patients with asthma is not helpful unless they are symptomatic for GERD and/or they have severe nocturnal symptoms. You should start with once a day dosing, titrate to the lowest effective doses, and if the patient is still not responsive, consider additional testing.

**Chronic Cough**

Chronic cough is defined as a cough that is present for more than 8 weeks. As we all know, the most common causes of chronic cough include postnasal drip, asthma, GERD, chronic bronchitis, and ACE inhibitor use. These 5 entities represent 90% of the cases of chronic cough and the list can be paired down to 3 if the patient has a normal chest x-ray and is not taking an ACE inhibitor. Jacobs et al. looked at the cause of chronic cough as it relates to reflux and found that it is either direct irritation of the respiratory tract by aspiration or a vagally mediated stimulation of an esophageal-bronchial cough reflex or both. Ing et al. looked at the use of topical lidocaine swallowed into the esophagus and found that this significantly decreased cough suggesting the esophageal bronchial cough reflex certainly plays a role.

Seventy-five percent of patients with gastroesophageal reflux related cough do not exhibit typical reflux symptoms. Baldi et al. showed that specificity for the disease is with only 15% of patients undergoing EGD for chronic cough exhibiting esophagitis. Ours et al. showed that only 35% of patients with abnormal pH monitoring studies had a response to therapy. Therefore this disease is very difficult to deal with.

Treatment results have been mixed with this disease process. Poe et al. showed that 79% of patients with cough secondary to reflux responded to daily PPI therapy, but Baldi et al. only showed 60% resolution of symptoms. He also compared patients treated with lansoprazole 30mg BID for 4 weeks and then daily therapy for 12 weeks versus lansoprazole 30mg BID for 16
weeks and found no significant differences between the two groups based on symptoms of cough.

Therefore my recommendation would be to treat chronic cough patients with daily PPI therapy to start with for 3-4 months, and if they do not have any improvement you should reassess for other causes including postnasal drip, asthma, or chronic bronchitis, and get additional studies to determine the cause of the cough.

**Laryngopharyngeal reflux (LPR)**

As we discussed earlier, the symptoms of LPR compared to gastroesophageal reflux are often significantly different. In a position statement by the American Academy of Otolaryngology in 2002 by Koufman et al. the following differences were proposed to contrast the two disease processes.

<table>
<thead>
<tr>
<th>GERD</th>
<th>LPRD</th>
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<tr>
<td>Esophagitis Absent</td>
<td>Esophagitis Common</td>
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<tr>
<td>Daytime Symptoms</td>
<td>Nighttime symptoms</td>
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<tr>
<td>UES dysfunction</td>
<td>LES dysfunction</td>
</tr>
<tr>
<td>Short acid exposure</td>
<td>Prolonged acid exposure</td>
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<tr>
<td>Laryngeal irritation</td>
<td>Esophageal irritation</td>
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Below is a table outlining the signs and symptoms of LPR

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
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<tr>
<td>Hoarseness</td>
<td>Erythema of mucosa</td>
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<tr>
<td>Globus sensation</td>
<td>Vocal cord edema</td>
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<tr>
<td>Dysphagia</td>
<td>Interarytenoid pachydermia</td>
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<tr>
<td>Cough</td>
<td>Laryngeal mucous</td>
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<tr>
<td>Mucous production</td>
<td>Subglottic edema</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Granulomas</td>
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<tr>
<td>Halitosis</td>
<td></td>
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<td>Throat clearing</td>
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LPR is a very nonspecific disease process however. In a study by Milstein et al, 80-90% of normal patients will have reflux findings on laryngoscopy and Joniau et al. showed that 19-43% of normal volunteers will have hypopharyngeal reflux on pH monitoring. To make matters even more confusing, Koufman et al showed that LPR was documented by pH probe monitoring in only 50% of subjects despite 69% having symptoms. Therefore many physicians find the disease not only difficult to identify and quantify, but some don’t even believe in its existence given the variability in its presentation.
While I won’t go into the details of the LPR studies since this has been covered previously, the AAO position statement recommends twice a day PPI therapy compared to once a day PPI therapy based on several studies showing the benefit in LPR to those patients treated in this manner. This therapy should be continued for 6 months, plus or minus an H2 blocker before bed. Although this was the position statement in 2002, I think it is reasonable to start with once daily PPI therapy based off of studied seen in the chronic cough section, and then escalate to twice daily therapy if patients are still having symptoms. If patients do not respond to PPI therapy within 6 months additional studies should be ordered to search for another cause.

**Follow up and Additional Testing**

If patients have been adherent to treatment and their symptoms have responded to these syndromes, then you are in good shape and ready to take them off of their therapy. If patients have failed therapy then it is possible that they have resistant reflux or some other disease process that needs to be addressed.

Other causes of reflux type symptoms or symptoms that mimic the extra-esophageal syndromes could include eosinophilic esophagitis, non-acidic reflux (Pepsin), or esophageal disorders like achalasia, strictures, nutcracker esophagus or diffuse esophageal spasm. It could also be a combination of factors contributing to the clinical picture, but after empiric therapy, physiologic testing is required for non-responders.

One of the best tests that we have in our armamentarium includes either esophagogastroduodenoscopy (EGD) or transnasal esophagoscopy (TNE). The biggest benefit of these tests is the ability to directly visualize the mucosa. Strictures, Barrett’s esophagus, and esophageal ulcers/polyps can be biopsied and diagnosed. Unfortunately, you will not always see esophagitis in patients with LPR symptoms.

The normal endoscopic exam will show smooth mucosa, prominent submucosal vessels, and a whitish pink color. Common findings of eosinophilic esophagitis can include: crepe paper mucosa, friability, shearing, edema, white plaques, linear furrowing, small caliber esophagus, concentric mucosal rings, and strictures. Linear furrowing will be present in 25 to 100% of patients and loss of vascularity occurs in about 93% of patients. It is important to differentiate between GERD and eosinophilic esophagitis. GERD may present with linear furrowing similar to that seen in eosinophilic esophagitis however there will also likely be a distal component of ulceration near the gastroesophageal junction. Strictures associated with eosinophilic esophagitis tend to occur both proximally and distally whereas isolated distal strictures are more commonly seen in reflux.

Twenty-four hour dual probe pH testing is another physiologic test that can be extremely helpful in determining whether reflux is present or not. It is generally reserved for those patients who have failed therapy or if the diagnosis is unclear. With this study you have the ability to quantify the number and duration of reflux episodes that occur as well as the pH drop that people experience. You can have patients record sleep and wake periods to differentiate upright and supine situations and you can even correlate events with symptoms if patients keep a diary of
exactly when they are feeling their worst. There is no consensus on what exactly qualifies as LPRD at the upper probe, however 1-4 events/hour is generally considered the normal range.

Intraluminal Impedance is a relatively new study used to measure the resistance changes in the esophagus. The interesting thing about impedance testing is that it can actually measure and record directional changes in resistance to gases, liquids, or solid boluses in the esophagus. So things like belching and non-acidic reflux can be measured with this test. You can even measure the height or level of reflux within the esophagus. Finally intraluminal impedance can be combined with pH monitoring to determine the type of reflux that is occurring to help determine if PPI therapy will be useful.

Esophageal Manometry is a great measure of peristalsis and esophageal sphincter pressure. It can help identify esophageal sphincter dysfunction and it has been shown to change the surgical plan in patients undergoing a Nissen fundoplication in up to 10% of cases if a motility disorder is present. Ultimately this is one of the best physiologic studies of the esophagus especially in patients complaining of dysphagia as part of their reflux constellation of symptoms.

Because manometry has the ability to determine esophageal sphincter tone it is also quite useful in differentiating esophageal disorders. First of all, diffuse esophageal spasm is a non-peristaltic disorder, and therefore there will be no propagation of the esophageal wave. Scleroderma and achalasia look very similar until you evaluate the lower esophageal sphincter and notice that patients with low resting LES tone have scleroderma whereas patients with achalasia have a very high LES tone. Therefore esophageal manometry can be very helpful in determining esophageal pathology.

Finally one study that has been around for many years but is still clinically useful is an upper GI series with contrast. This study can help identify strictures, polyps, obstructions, and some motility disorders strictly on the appearance of the esophagus. It can also identify hiatal hernias and help to qualitatively evaluate esophageal peristalsis.

When to Refer for Surgery?

As I discussed at the beginning, it is often hard to determine who is appropriate for surgical referral and when they should be referred for treatment. In this next section we will discuss surgical indications for treatment of reflux and present outcomes based on those surgical procedures.

The Nissen fundoplication was first described by Rudolf Nissen, MD in the 1950’s. The procedure involves wrapping the fundus of the stomach around the esophagus proximally thus giving additional support to the LES and preventing acid into the esophagus. Recently the laparoscopic approach to the Nissen procedure has taken favor over the open approach. Stefanidis et al. commented that the laparoscopic procedure produces improved cosmesis, reduced morbidity, decreased hospital stay, decreased respiratory complications, and faster recovery.
In 2008 the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) came out with a position statement on gastroesophageal reflux disease and the indications for surgical therapy. Reflux was defined as positive pH probe testing, peptic strictures that have been biopsied with no malignancy present, Barrett’s Esophagus on biopsy, or mucosal breaks on endoscopy. These were grade A recommendations.

With regards to pH probe studies, patients need to be free from PPI and H2 blockers for at least 2 weeks. The most important measurement is the total time with pH<4 at 5cm above the LES. Other parameters evaluated are total esophageal acid exposure, upright acid exposure, supine acid exposure, number of episodes, number of episodes lasting >5 minutes, and duration of the longest episode.

In addition to other studies, there is no need for mandatory preoperative manometry however it can be helpful to identify achalasia or other surgery modifying abnormalities as discussed earlier. Barium swallow is not mandatory prior to surgery but can be helpful to delineate anatomy and potentially identify a hiatal hernia that can be repaired at the same time as surgery. Gastric emptying studies are not helpful or necessary preoperatively.

After a patient has been diagnosed with reflux, indications for a Nissen procedure includes:

1. Failed medical management
2. Patient request for surgery over medical management
3. Complications of GER including peptic stricture and Barrett’s esophagus
4. Extraesophageal manifestations of reflux resistant to therapy

Francis et al. looked at predictors of success in 237 patients with extra-esophageal reflux that were resistant to medical therapy. Only 27 of these patients were treated with a Nissen fundoplication based on objective reflux findings. All patients were evaluated preoperatively with Manometry, Impedance, EGD and pH monitoring. They showed that 59% of patients had at least a partial improvement in symptoms but better results were seen in patients who had heartburn +/- regurgitation at the initial visit, those patients with a hiatal hernia, and those patients with pH<4 for more than 12% of the time. Manometry, Impedance, and EGD did not predict success.

Lundell et al. looked at the difference between patients treated with medical versus surgical therapy. It was a RCT with 155 patients in each arm. At 12 years follow up there were 71 remaining patients in the medical group and 53 in the surgical group. They reassessed patients based on EGD and symptomatology. Although numbers were much smaller than the initial trial, 53% of patients treated with surgery were still in remission compared to only 40% of patients treated with medical therapy. Therefore it was their belief that surgery was superior to medical therapy.

A Cochran review also looked at the comparison between medical and surgical therapy. In 2010 Wileman et al. included 4 RCT’s and over 1200 patients with primary outcomes
evaluated including reflux specific QOL surveys, heartburn, regurgitation, and dysphagia. They found that surgery was superior to medical therapy postoperatively, at 3 months and 1 year after surgery on QOL measures. Surgery was more costly with a low complications rate of 1.7%, however a small percentage of patients have persistent dysphagia after surgery at 4.6%. Medical therapy was more likely to result in persistent heartburn or regurgitation.

Several cost effectiveness studies have been performed comparing surgery and medical therapy. In 2001 Thijssen et al. performed a systematic review of 4 articles looking as cost effectiveness. 2 articles favored medical management stating lower initial costs and more symptom free months however 2 studies favored surgery citing more quality adjusted life years than PPI therapy. Limitations of the discussed studied were than they looked strictly from a 3rd party payer point of view not taking into account changing costs over time and most of these studies were not long term evaluation. Therefore more long term data is needed.

Innovative Therapy

Although surgery has been established as the treatment choice for failed antireflux therapy, I think it’s important to look back at the proximal problem of the disease which is dysfunction of the LES. GABA agonists like baclofen have shown excellent results and preventing LES hypotension and decreasing reflux events. The problems with these medications involved poorly tolerated central effects like sedation. Therefore development of peripherally acting GABA agonists are being developed and have shown some good results in trials when combined to PPI therapy.

Conclusions

Although there is a clear association between reflux and the previously mentioned extra-esophageal syndromes however causation data is limited. Therefore a conservative approach with empiric therapy can be helpful prior to ordering expensive tests. If patients continue to be symptomatic then a formal workup with pH and EGD studies to rule reflux in or out is instituted. Other tests like impedance and manometry should be reserved for patients with more esophageal problems and are not predictive or necessary prior to surgical therapy. Referral to surgeons for a Nissen fundoplication should be considered in all patients with documented reflux that are resistant to therapy, have proven complications or reflux or do not wish to take medications for life. Alternative therapies addressing the LES are on the horizon but are not yet accepted or proven equivalent. More studies are needed to examine their significance.
References