Reflux: Beyond the Burn

Internal Medicine Grand Rounds

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Purpose & Overview:
Gastroesophageal reflux disease (GERD) is very common in the United States, affecting 20-40% of the population. There is an additional portion of patients with atypical reflux symptoms, including pulmonary and otolaryngology manifestations of disease, known as extra-esophageal reflux (EER). This presentation reviews the current data around the pathophysiology, clinical features, evaluation and management of EER.
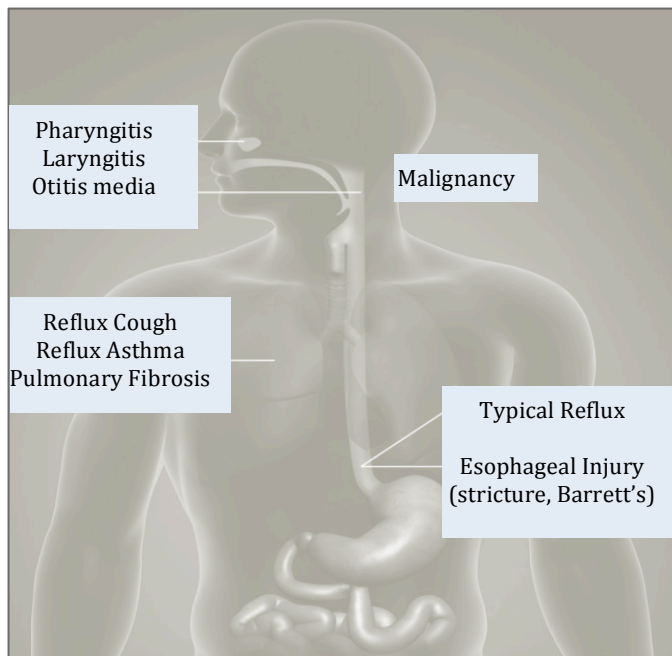
Educational Objectives:
1. To recognize extra-esophageal reflux (EER) and the current pathophysiologic explanation for EER.
2. To review the data linking EER with chronic cough, asthma and laryngitis.
3. To develop a treatment approach to EER including the role of GI diagnostic testing and use of PPIs.

Introduction to GERD and Extra-Esophageal Reflux (EER)

Gastroesophageal reflux disease (GERD) is the presence of stomach contents in the esophagus and the subsequent development of troublesome symptoms or complications.[1] GERD is very common in the United States, affecting 20-40% of the population and is on the rise with the aging population and obesity epidemic[2].

Typical symptoms attributed to GERD include heartburn and regurgitation. However, it is now recognized that there are additional atypical symptoms of GERD including chronic cough, laryngitis and asthma, as well as proposed associations of chronic lung disease, otitis media and even upper airway malignancy. These less common presentations of reflux are collectively known as extra-esophageal reflux (EER) and can occur with or without typical GERD symptoms[1]. While typical GERD carries a high cost of treatment, 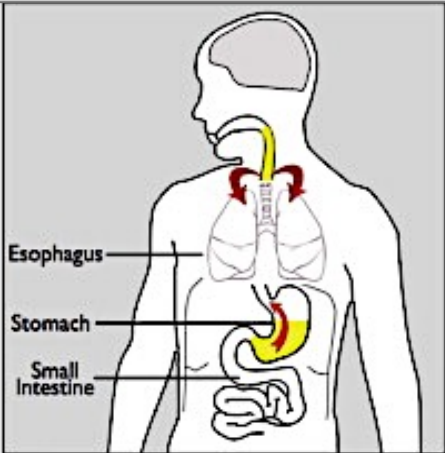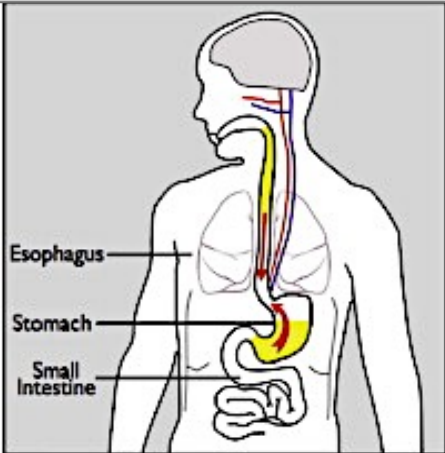already ranging from $9-12 billion, recent data suggests that the cost associated with the treatment of patients with EER reaches upwards of $50 billion[3] – up to 5 times that of GERD. This is largely attributed to the fact that a diagnosis of EER is often difficult to achieve due to a lack of diagnostic criteria and testing values. Moreover, there remains controversy regarding the causation versus correlation of these diseases as they are common diseases and may co-exist. Even if a diagnosis of EER is made, there is a paucity of data describing effective treatments for these symptoms. Despite this lack of decisive signs or symptoms, EER has become a primary diagnosis offered by otolaryngologists, allergists, gastroenterologists, and primary care physicians, and has resulted in many patients being given a barrage of medications, undergoing diagnostic tests, and even surgeries[4]. This ongoing controversy around EER is the subject of this review.

Pathophysiology of EER

GERD is accepted as causing esophageal damage largely via direct caustic injury to the mucosa. With EER however, there are currently two pathophysiologic pathways of injury – direct aspiration of gastric contents which is similar to typical GERD (reflux theory) and indirect damage via vagally mediated mechanisms (reflex theory)[5].

Direct Injury: The body offers several layers of protection from gastric contents including the upper and lower esophageal sphincters (UES and LES respectively). In the physiologic state, the LES allows for some refluxate to enter the esophagus but the elevated UES basal pressure usually prevents laryngeal and pharyngeal exposure to gastric contents[3]. The esophagoglottic closure reflex and swallowing or cough help to clear escaped refluxate and prevent a breach of the airway. It is hypothesized that dysfunction in any of these protective measures could contribute to the complications of EER.[3] Micro-aspiration of gastric (or duodenal) contents has been shown to cause damage to the upper respiratory tract including the pharynx, larynx and lungs[6] by way of acid, pepsin and bile acids. Furthermore, there is evidence of microbial contamination of aspirated contents resulting in pulmonary complications such as asthma or pulmonary fibrosis[5].

Indirect Injury: When refluxate enters the distal esophagus, this results in vagally mediated bronchoconstriction and cough, thought to be a consequence of a shared embryonic origin[3] between the esophagus and bronchial tree. The acidification of the distal esophagus also stimulates acid-sensitive receptors that can lead to non-cardiac chest pain. More recent studies have reported reflux esophagitis in a rat model developing from a cytokine-mediated inflammatory injury where refluxed acid and bile stimulate the release of inflammatory cytokines from esophageal squamous cells and recruitment of lymphocytes[7]. This cytokine-mediated response may also play a role in EER.

Pathophysiology of Extra-Esophageal Reflux	
Reflux Theory	**Reflex Theory**
- reflux through esophageal sphincters causing pulmonary, laryngeal, pharyngeal or extraesophageal symptoms - direct contact of gastric reflux with bronchial and laryngeal areas	- reflux into distal esophagus stimulates vagally-mediated reflex - common embryonic origin between esophagus and bronchial tree

Established Associations with EER

Chronic Cough

Cough is the single most common reason for PCP visits in the US and is a common reason for referral to subspecialists such as Pulmonary, Allergy and GI. Chronic cough has a well-established association with GERD and it is well documented that in the absence of smoking and ACE inhibitors, the most common causes of cough are upper airway cough syndrome (UACS), Asthma and GERD[8]. The cough associated with GERD is often described as nonproductive and is not responsive to medications such as antitussives, antibiotics or even reflux treatment. Patients describe sudden attacks triggered by eating or talking and seem to result from a lowered response threshold to stimuli. The attacks are exacerbated in the post-prandial state, at night and in the supine position. Episodes can result in oculorrhea, rhinorrhea, vomiting, laryngospasm and syncope or near-syncope[9]. There are several large population-based surveys demonstrating increased risk of chronic cough amongst patients with reflux symptoms or esophagitis. Similarly, studies have shown a high prevalence of objective signs of GERD in patients with chronic cough. For example, Alhabib et al demonstrated pathologic esophageal acid exposure in 52% of patients with chronic cough[10]. Patients however, will often not report typical GERD symptoms and lack of these symptoms cannot be used to exclude reflux as the cause of chronic cough.

Further complicating the evaluation of GERD as the etiology of chronic cough is the lack of directed testing. Endoscopy can offer objective findings in patients with typical reflux including esophagitis and Barrett's esophagus. Patients with chronic cough as the presenting symptom however, have a low prevalence of these findings and the presence of such findings is not diagnostic of this syndrome[3]. It has been suggested that in the patient with chronic cough of unclear etiology, upper endoscopy, esophageal manometry, gastric emptying test, and upper gastrointestinal radiography should be completed to exclude malignancy and achalasia[11]. Additionally, pH with impedance monitoring offers the ability to correlate esophageal reflux episodes with cough symptoms. This is particularly useful in patients in whom GERD is suspected but treatment does not eliminate the cough.

Despite the widely advocated role of GERD in chronic cough, there is a paucity of RCT data on how effective GERD treatment is in improving symptoms[12]. Practically speaking and expert opinion suggest that an empiric trial with acid-suppressive medications, such as PPIs, is a reasonable recommendation in those without alarm signs or symptoms. This is particularly true in the presence of concomitant symptoms of GERD. Empiric PPI therapy occurs in the form of twice daily PPI therapy for two months as an adequate trial to assess for symptom response. In the event that the patient has a positive response of their laryngeal signs and symptoms, one should taper to once-daily PPI in the morning, followed by intermittent PPI or treatment with H2RAs. In those
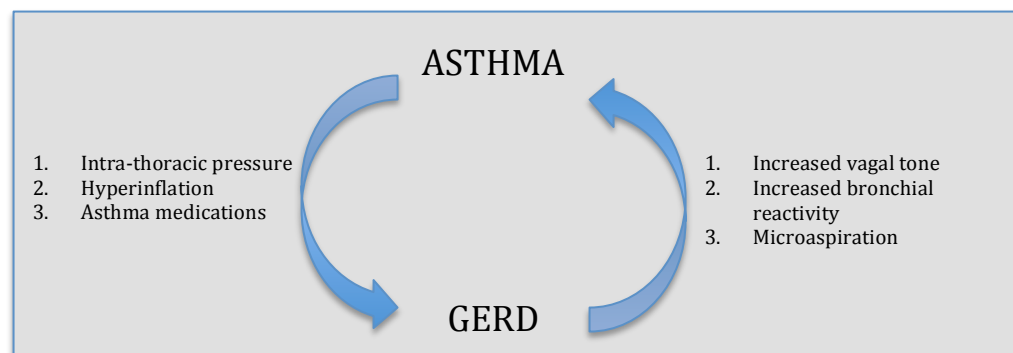
unresponsive to PPI therapy, further diagnostic testing may be pursued[11].

Asthma:

Many studies have tried to define the relationship between asthma and GERD. While GERD is present in up to 80% of patients with asthma based on pH studies and can often occur without typical reflux symptoms[13], what remains uncertain is whether this relationship is a causal or correlate. There is evidence that when treated, GERD symptoms can be associated with improvements in some but not all objective pulmonary function measurements.

It is theorized that the GERD may induce bronchoconstriction and asthma through increased vagal tone (reflex), acidification of the distal esophagus resulting in increased bronchial reactivity, and/or microaspiration of refluxate (reflux)[3]. This is corroborated by studies demonstrating infusion of acid into the distal esophagus causes airway inflammation in a temporal manner. There is also data to support that asthma induces GERD by way of changes in intra-thoracic and intra-abdominal pressure, and hyperinflation altering the relationship of the gastroesophageal junction with the crural diaphragm. Asthma medications themselves can also decrease the LES pressure and worsen reflux.

Given the ability to avoid unpleasant testing and the potential for progression to chronic lung disease with untreated symptoms[11], experts argue that an empiric trial of PPI for 2-3 months is reasonable when GERD contributing to symptoms is suspected, particularly in those with concomitant typical GERD symptoms. Although a large meta-analysis found that there is insufficient evidence to support the routine use of PPIs in the treatment of asthma[14], treatment with PPI is reported to reduce nocturnal symptoms[15], and in some studies, reduce asthma exacerbations and improve quality of life elated to asthma[16]. This is further corroborated by studies demonstrating improvement of asthma exacerbations following PPI therapy or surgical treatment for reflux with Nissen fundoplication[15,17]. As with chronic cough, in those patients who are unresponsive to an empiric trial of acid suppression, testing for reflux by pH or impedance monitoring, may be needed and/or consideration of alternative diagnosis.

ASTHMA

1. Intra-thoracic pressure
2. Hyperinflation
3. Asthma medications

1. Increased vagal tone
2. Increased bronchial reactivity
3. Microaspiration

GERD

Laryngopharyngeal Reflux:

Laryngopharyngeal reflux (LPR) involves the reflux of gastroduodenal contents into the larynx causing inflammation and symptoms resulting in laryngitis[18]. Reports suggest that up to 10% of patients presenting to otolaryngologists present with symptoms related in part to GERD, including hoarseness, sore or burning throat, chronic cough or throat clearing, globus, postnasal drip, laryngospasm, and even laryngeal neoplasm. These symptoms can be attributed to GERD as a primary or contributing factor in up to 60% of patients with hoarseness as a symptom[18].   Laryngeal pathology is thought to result from refluxate damaging the laryngeal tissue and producing localized symptoms[19]. LPR is not usually associated with typical GERD symptoms or endoscopic findings of reflux.   Instead, patients often report daytime or upright symptoms rather than nocturnal or supine symptoms. The lack of a pathognomonic finding has lead to the development of two reflux-scoring systems to be used clinically to help identify LPR. The reflux symptom index (RSI) is a 9 item symptom based instrument for patients with LPR that accurately documents symptom and improvement over time, with a value of >13 considered significant[20]. The Reflux Finding Score (RFS) is an 8-item clinical severity scale that encompasses the most common laryngeal findings on laryngoscopy and a value >7 is suggestive of LPR[16]. It is important to note that findings during laryngoscopy are highly subjective, with some studies showing only a 50% correlation of LPR and abnormal esophageal acid exposure, and can be present in up to 80% of normal subjects without GERD[3].   The American College of Gastroenterology (ACG) guideline on management of GERD states that a "diagnosis of reflux laryngitis should not be made solely on laryngoscopic findings and that reflux testing should be pursued prior to initiating empiric treatment with PPIs in laryngitis patients who do not have concomitant GERD symptoms".[21]

Arabic reflux symptom index as designed by Farahat *et al.* [12]		Reflux finding score as designed by Belafsky *et al.* [10]	
Finding		Finding	Score
Within the last month, how did the following problems affect you?	0 = no problem, 5 = severe problem	Subglottic edema	2 = present, 0 = absent
		Ventricular obliteration	2 = partial, 4 = complete
		Erythema/hyperemia	2 = arytenoids only, 4 = diffuse
Hoarseness or a problem with your voice	0 1 2 3 4 5	Vocal cord edema	1 = mild, 2 = moderate, 3 = severe, 4 = polypoid
Clearing your throat	0 1 2 3 4 5		
Excess throat mucus or postnasal drip	0 1 2 3 4 5	Diffuse laryngeal edema	1 = mild, 2 = moderate, 3 = severe, 4 = obstructing
Difficulty swallowing food, liquids, or pills	0 1 2 3 4 5		
Coughing after you ate or after lying down	0 1 2 3 4 5	Posterior commissure hypertrophy	1 = mild, 2 = moderate, 3 = severe, 4 = obstructing
Breathing difficulties or choking episodes	0 1 2 3 4 5		
Troublesome or annoying cough	0 1 2 3 4 5	Granuloma/granulation	2 = present, 0 = absent
Sensations of something sticking in your throat or a lump in your throat	0 1 2 3 4 5	Thick endolaryngeal mucus/other	2 = present, 0 = absent
Heartburn, chest pain, indigestion, or stomach acid coming up	0 1 2 3 4 5	Total	
Total = 45			

While the esophageal mucosa may be somewhat equipped to handle the insult associated with reflux, it has been suggested that the upper and lower airway are more vulnerable to direct harm. Failing to recognize and treat LPR can lead to unnecessary medical costs, prolonged symptoms and delayed healing of inflamed tissues with subsequent complications. It has also been found that LPR
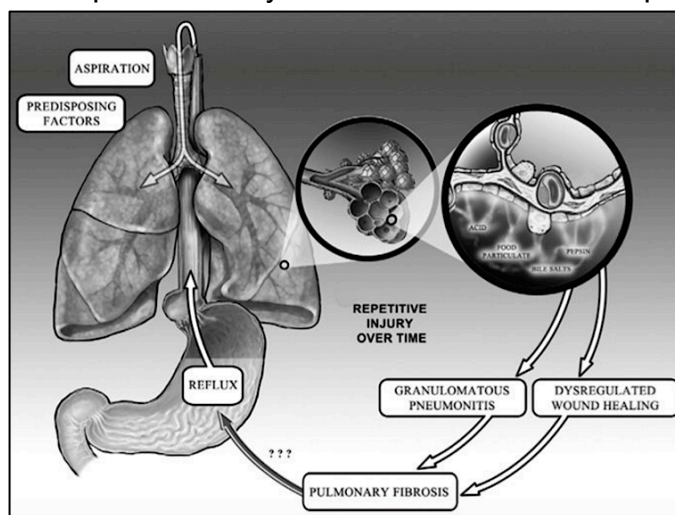
symptoms are more prevalent in patients with esophageal adenocarcinoma than are typical GERD symptoms[22]. The difficulty associating LPR with GERD lies in the fact that typical LPR symptoms are non-specific and can be caused by a myriad of triggers including infection, allergy, smoking and environmental irritants[19].

Given the diagnostic difficulty and concern for ongoing tissue damage, it seems reasonable to empirically offer acid-suppressive therapy in LPR even though the benefits are not very well proven by the controlled studies. A meta-analysis of RCTs in suspected GERD-related LPR, found a non-significant symptom reduction with PPI compared with placebo but there was a high placebo response noted as well as a lack of significant clinical predictors of response.[23] In order to confirm the diagnosis of LPR, one can assess the response to lifestyle and medical therapy with PPI, assess for endoscopic evidence of mucosal healing, or demonstrate reflux via pH monitoring and a correlation to symptoms[19]. In situations where acid-suppression does not eliminate symptoms or laryngoscopic findings, impedance monitoring for remaining acid reflux and non-acid reflux may be of value.

Proposed Associations with EER

Idiopathic Pulmonary Fibrosis:

Idiopathic pulmonary fibrosis (IPF) is a relentlessly progressive scarring disorder of the lungs characterized by dyspnea, cough, and ultimately, respiratory failure. The prevalence of IPF is estimated at between 14 and 42.7 per 100,000 with increasing disease prevalence[3]. Based on pH monitoring, GERD is highly prevalent in patients with IPF yet almost half of those with both disease states are asymptomatic from a GI symptom perspective. Increasing evidence suggests that microaspiration of gastric contents may be an inciting factor for repetitive lung injury and ultimately lead to the development of IPF[24]. A retrospective analysis of two cohorts of ILD pat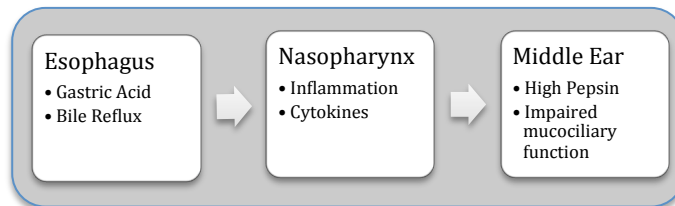ients found 47% reported current treatment with GER medications[24]. Chronic lung disease patients demonstrate more severe reflux parameters than their LPR counterparts. One study showed lower mean nocturnal baseline impedance (a novel measure of esophageal mucosal integrity), suggesting more severe reflux, as well as a higher proportion of weak swallows noted on HRM[1]. Thus it has been suggested that earlier esophageal function

testing and reflux intervention may be indicated in these patients with suspected lower airway manifestations of GERD. Adjusted analysis demonstrated that the use of GERD medications was an independent predictor for longer survival time and a lower radiologic fibrosis score[24]. Furthermore, two retrospective case series showed stabilization of pulmonary function and oxygen requirements with medical and surgical management of GERD[13,15].
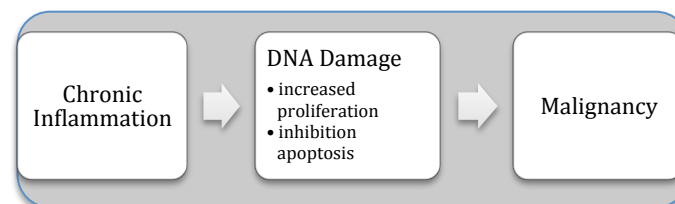
Otitis Media:

With reflux of gastroduodenal contents into the upper airway, it has been demonstrated that adults can also have refluxed contents in their middle ears and accompanying Eustachian tube dysfunction[2].

As previously described, there is direct injury via activated pepsin and acid in the supraesophageal region which may lead to chronic otitis media through an inflammatory reaction and, possibly, secondary infection[2]. These findings suggest that the presence of reflux might be more prevalent than expected in adult patients with otitis media of no clear cause. Published literature concerning reflux and otitis media in adults however, is limited to clinical case series and the evaluation of more cases that could be diagnosed as reflux-induced otitis media is necessary for better understanding of the disease entity.

Malignancy:

Chronic inflammation in reflux esophagitis is known to create a favorable environment for DNA damage, increased proliferation, and inhibition of apoptosis[25].

In a study by Reavis et al comparing a cohort of patients with esophageal adenocarcinoma and control groups with Barrett's, GERD, and non-GERD patients, the authors demonstrated the prevalence of LPR was significantly higher in patients with esophageal carcinoma compared to all control groups and this prevalence of LPR progressively increased from the non-GERD, GERD, Barrett's, and esophageal adenocarcinoma groups[22]. This suggests that those with LPR may have increased inflammatory damage. Again working under the premise that the laryngopharyngeal mucosa is more susceptible to damage by gastric refluxate and a lack of intrinsic defense mechanisms present in their esophageal counterparts (such as peristalsis, saliva, and bicarbonate production), it is plausible that chronic uncontrolled LPR could not only cause inflammatory, but perhaps also neoplastic, changes in the laryngopharynx, as it does in the esophagus[25]. Furthermore, Cekin et al. reported LPR in 69.8% of new patients presenting with a laryngeal lesion and that there was a significant

relationship between LPR positivity (measured by the RSI) with the presence of an upper esophageal and pharyngeal cancer[26]. It has also been shown that patients with LPR have pepsin mediated laryngeal mucosal injury, including dilation of intracellular spaces (DIS) and mitochondrial damage[25]. This direct role of pepsin in mucosal damage may explain the lack of improvement with acid-suppressive medication, as the acidity of the refluxate may not be as clinically relevant[25].

Role of GI Diagnostics and Treatment

According to the current data, the available diagnostic tools to establish GERD as the cause of EER symptoms have serious limitations and have failed to show a clear therapeutic benefit of PPIs in treating all-comers with EER[21].

EGD:
The presence of EER symptoms can be an indication for upper endoscopy. This is generally performed early on in the evaluation of a patient with typical symptoms of GERD but may occur later in the course of care in patients with EER in the absence of heartburn or regurgitation. Upper endoscopy can document the presence of GERD when esophagitis or another GERD related complication is seen but this is only found in one third of patients with GERD symptoms and is even rarer in those with EER[21].

Ambulatory pH and Impedance Testing:
The pH monitoring system can be used to diagnose GERD by confirming the presence of pathologic amounts of reflux into the esophagus. In order to detect acid exposure to the UES, a proximal probe usually is placed distal to the UES. When this is combined with MII, which can identify liquid, gas, and mixed forms, one can detect both acid and nonacid reflux by the UES. Importantly though, the presence of pathologic amounts of reflux does not establish GERD as the cause of EER symptoms. Multiple studies demonstrate the lack of standard normative values and poor correlation with results and response to acid suppression[3]. The TOPPITS (Trial of PPI in Throat Symptoms) trial is ongoing and its conclusions may help provide insight into the treatment of these patients. Ambulatory pH monitoring is useful in excluding the presence of pathologic amounts of reflux, especially in the setting where EER symptoms do not correlate with episodes of reflux activity.

Empiric Therapy:
There is a lack of evidence to support empiric PPI therapy in all patients with EER yet this remains common practice amongst several specialists. Given the recent associations of PPI therapy with adverse side effects such as osteoporosis and renal injury, it is imperative to ensure treatment of appropriate patients. A meta-analysis of nine randomized controlled trials found no
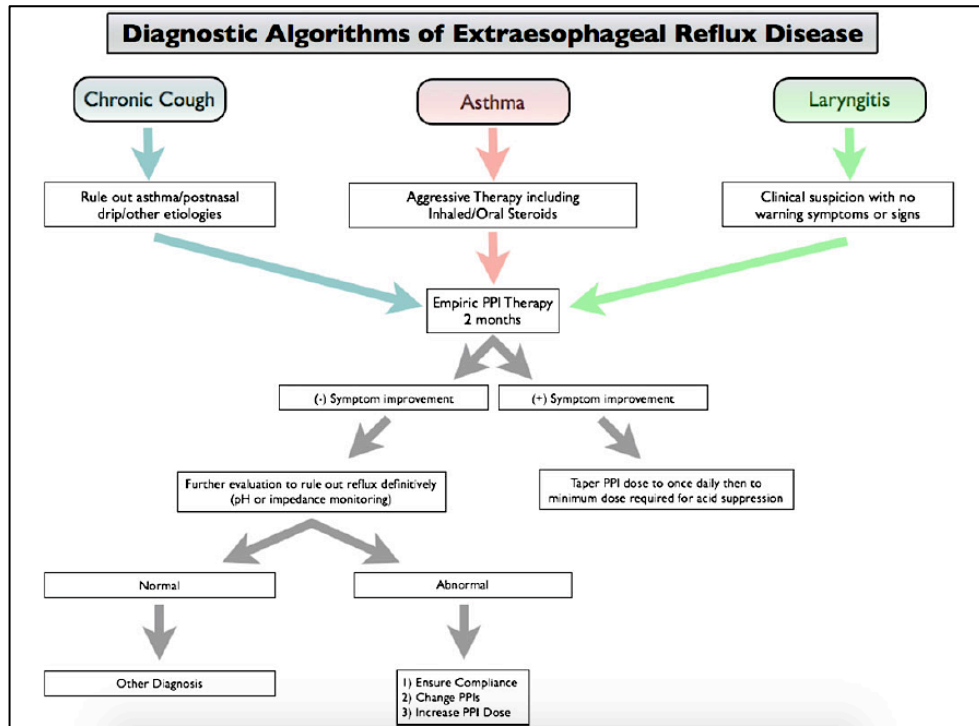
advantage for PPI compared with placebo for treatment of chronic cough (OR 0.46, 95% CI 0.19-1.15) though there was an improvement in cough scores[12]. In terms of asthma, there is data to suggest a modest improvement in peak expiratory flow measurements but this may not be of meaningful clinical significance[14]. This is also true of the data for treating LPR with PPIs where a meta-analysis found no significant advantage over placebo for treating GERD-related chronic laryngitis (RR 1.28, 95% CI 0.94-1.74)[21] This is in contrast to the American Academy of Otolaryngology's position statement on LPR which states that "Expert opinion and clinical experience support the use of high-dose proton pump inhibitor therapy (often two to four times the dose recommended routinely for treatment of distal gastroesophageal reflux disease (GERD), for prolonged periods of time. Surgery to control reflux may be necessary in some patients with LPR". The GI guidelines state that PPI therapy is reasonable in patients with EER and typical symptoms of GERD or objective evidence of GERD but that "routine treatment in those with EER and a lack of GERD symptoms cannot be routinely recommended"[21]. Furthermore for those patients that are treated with PPI and who do not respond to a 2-3 month course of therapy, should be evaluated as "refractory GERD" including the exclusion of alternate etiologies[21].

Alternate Diagnosis:
Finally, one should recognize that not all cough, asthma or laryngitis is reflux mediated. These are all common diagnoses that may co-exist or be the result of multiple causes. While a positive response of symptoms to acid suppression is helpful, a lack of response is less clear. It may be that the symptoms can be attributed to reflux or it may be that the patient suffers from an alternative cause of symptoms, including functional disorders. Studies suggest beneficial symptomatic response of this group of patients to neuromodulator medications such as amitriptyline (10 mg/d), gabapentin (100 to 900 mg/d), and pregabalin (150 mg bid maximum)[3]. Additionally, there is likely additional pathophysiology that is not yet understood in terms of reflux, especially as it pertains to EER, mechanism of injury and delineating which patients would benefit from what type of intervention.

Conclusion
GERD is a prevalent disease with an additional burden of EER being better recognized. This discussion should increase one's awareness of EER and its role in chronic cough, asthma and laryngitis as well as its potential contribution to IPF, otitis media and even malignancy. While it remains controversial, empiric therapy with acid-suppressive medications is a reasonable initial treatment of choice in those without warning symptoms, particularly if they have associated GERD symptoms. Diagnostic testing with pH and/or impedance monitoring is appropriate in those unresponsive to empiric acid suppression. There remains a paucity of causal evidence for GERD and EER, and in those unresponsive to aggressive acid suppression, alternative diagnosis should be considered.

Diagnostic Algorithms of Extraesophageal Reflux Disease

Chronic Cough → Rule out asthma/postnasal drip/other etiologies

Asthma → Aggressive Therapy including Inhaled/Oral Steroids

Laryngitis → Clinical suspicion with no warning symptoms or signs

Empiric PPI Therapy 2 months

(-) Symptom improvement

(+) Symptom improvement

Further evaluation to rule out reflux definitively (pH or impedance monitoring)

Taper PPI dose to once daily then to minimum dose required for acid suppression

Normal

Abnormal

Other Diagnosis

1) Ensure Compliance
2) Change PPIs
3) Increase PPI Dose

References

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus G. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol.* 2006;101(8):1900-1920; quiz 1943.
2. Sone M, Kato T, Nakashima T. Current concepts of otitis media in adults as a reflux-related disease. *Otol Neurotol.* 2013;34(6):1013-1017.
3. Hom C, Vaezi MF. Extra-esophageal manifestations of gastroesophageal reflux disease: diagnosis and treatment. *Drugs.* 2013;73(12):1281-1295.
4. Ates F, Vaezi MF. Approach to the patient with presumed extraoesophageal GERD. *Best Pract Res Clin Gastroenterol.* 2013;27(3):415-431.
5. Wang Z, Hu Z, Wu J, et al. Insult of gastroesophageal reflux on airway: clinical significance of pharyngeal nozzle. *Front Med.* 2015;9(1):117-122.
6. Mitchell DR, Derakhshan MH, Robertson EV, McColl KE. The Role of the Acid Pocket in Gastroesophageal Reflux Disease. *J Clin Gastroenterol.* 2016;50(2):111-119.
7. Souza RF. From Reflux Esophagitis to Esophageal Adenocarcinoma. *Dig Dis.* 2016;34(5):483-490.
8. Pratter MR. Overview of common causes of chronic cough: ACCP evidence-based clinical practice guidelines. *Chest.* 2006;129(1 Suppl):59S-62S.
9. Yuksel ES, Vaezi MF. Therapeutic strategies for laryngeal manifestations of gastroesophageal reflux disease. *J Clin Gastroenterol.* 2013;47(3):195-204.
10. Alhabib KF, Vedal S, Champion P, Fitzgerald JM. The utility of ambulatory pH monitoring in patients presenting with chronic cough and asthma. *Can J Gastroenterol.* 2007;21(3):159-163.
11. Adamali HI, Maher TM. Current and novel drug therapies for idiopathic pulmonary fibrosis. *Drug Des Devel Ther.* 2012;6:261-272.
12. Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database Syst Rev.* 2011(1):CD004823.
13. Harding SM, Guzzo MR, Richter JE. The prevalence of gastroesophageal reflux in asthma patients without reflux symptoms. *Am J Respir Crit Care Med.* 2000;162(1):34-39.
14. Chan WW, Chiou E, Obstein KL, Tignor AS, Whitlock TL. The efficacy of proton pump inhibitors for the treatment of asthma in adults: a meta-analysis. *Arch Intern Med.* 2011;171(7):620-629.
15. Kiljander TO, Harding SM, Field SK, et al. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. *Am J Respir Crit Care Med.* 2006;173(10):1091-1097.
16. Littner MR, Leung FW, Ballard ED, 2nd, Huang B, Samra NK, Lansoprazole Asthma Study G. Effects of 24 weeks of lansoprazole therapy on asthma symptoms, exacerbations, quality of life, and pulmonary function in adult asthmatic patients with acid reflux symptoms. *Chest.* 2005;128(3):1128-1135.

17. Sontag SJ, O'Connell S, Khandelwal S, et al. Asthmatics with gastroesophageal reflux: long term results of a randomized trial of medical and surgical antireflux therapies. *Am J Gastroenterol.* 2003;98(5):987-999.
18. Vaezi MF, Hicks DM, Abelson TI, Richter JE. Laryngeal signs and symptoms and gastroesophageal reflux disease (GERD): a critical assessment of cause and effect association. *Clin Gastroenterol Hepatol.* 2003;1(5):333-344.
19. Ford CN. Evaluation and management of laryngopharyngeal reflux. *JAMA.* 2005;294(12):1534-1540.
20. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice.* 2002;16(2):274-277.
21. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2013;108(3):308-328; quiz 329.
22. Reavis KM, Morris CD, Gopal DV, Hunter JG, Jobe BA. Laryngopharyngeal reflux symptoms better predict the presence of esophageal adenocarcinoma than typical gastroesophageal reflux symptoms. *Ann Surg.* 2004;239(6):849-856; discussion 856-848.
23. Qadeer MA, Phillips CO, Lopez AR, et al. Proton pump inhibitor therapy for suspected GERD-related chronic laryngitis: a meta-analysis of randomized controlled trials. *Am J Gastroenterol.* 2006;101(11):2646-2654.
24. Loomis-King H, Flaherty KR, Moore BB. Pathogenesis, current treatments and future directions for idiopathic pulmonary fibrosis. *Curr Opin Pharmacol.* 2013;13(3):377-385.
25. Bock JM, Howell AB, Johnston N, Kresty LA, Lew D. Upper esophageal and pharyngeal cancers. *Ann N Y Acad Sci.* 2014;1325:49-56.
26. Cekin E, Ozyurt M, Erkul E, et al. The association between Helicobacter pylori and laryngopharyngeal reflux in laryngeal pathologies. *Ear Nose Throat J.* 2012;91(3):E6-9.

27. NAEPP guidelines. www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf
28. Lo WK, Borges, LF, Chan WW et al. Differences in Motility and Reflux Profiles on esophageal function testing between upper and lower airway manifestations of Gastroesophageal Reflux Disease. *Gastroenterology.* 2016; 4:S1171