5 Diagnosis and Treatment of the Extraesophageal Manifestations of Gastroesophageal Reflux Disease

Feroze Sidwa, Alessandra Moore, Elaine Alligood, and P. Marco Fisichella

Introduction

Extraesophageal manifestations of gastroesophageal reflux disease (GERD) include cough, laryngopharyngeal reflux (LPR), and asthma. Both GERD and its extraesophageal manifestations are prevalent in clinical practice. In population-based studies, 19.8% of North Americans complain of typical symptoms of GERD (heartburn and regurgitation) at least weekly [1, 2]. Also in the late 1990s, GERD accounted for $9.3–$12.1 billion in direct annual healthcare costs in the United States, higher than any other digestive disease. As a result, acid-suppressive agents were the leading pharmaceutical expenditure in the United States. The prevalence of GERD in the primary care setting becomes even more evident when one considers that, in the United States, 4.6 million office encounters annually are primarily for GERD, while 9.1 million encounters include GERD in the top three diagnoses for the encounter. GERD is also the most frequently first-listed gastrointestinal diagnosis in ambulatory care visits [1, 2].

Extraesophageal manifestations of reflux have been estimated to cost $5438 per patient in direct medical expenses in the first year after presentation and $13,700 for 5 years. Estimates of the economic burden of extraesophageal reflux have shown that expenditures for extraesophageal manifestations of reflux could surpass $50 billion, 86% of which could be attributable to pharmaceutical costs [2]. Additionally, the National Health Care Survey carried out by the Center for Disease Control and Prevention has demonstrated that the chief complaint for primary care patient visits was cough in 6.1%, throat symptoms in 4%, and asthma in 2.8% [3]. Within these visits for cough, asthma and throat symptoms are contained the hidden prevalence of extraesophageal manifestations of GERD which to date have not been adequately addressed from a medical or surgical perspective due to their obscurity.

Distinguishing whether cough, LPR, and asthma are caused by GERD remains challenging for both the primary care physician and the specialist. This distinction is important because treatment of GERD with the intent of improving or curing extraesophageal manifestation can be ineffective. This review summarizes the current literature on extraesophageal manifestations of reflux to assist in clinical decision-making.

F. Sidwa, MD • A. Moore, MD • E. Alligood
Boston VA Healthcare System,
Harvard Medical School, Boston, MA, USA

P.M. Fisichella, MD, MBA, FACS (✉)
Brigham and Women's Hospital,
Harvard Medical School,
Boston VA Healthcare System,
1400 VFW Parkway, West Roxbury,
MA 02132, USA
e-mail: piero.fisichella@va.gov

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Clinical Presentation

Extraesophageal manifestations of GERD include cough, laryngopharyngeal reflux (LPR), and asthma. Chronic cough due to reflux is caused by gastric refluxate irritating the larynx and activating the afferent limb of the cough reflex. This is typically caused by direct irritation of the tracheobronchial tree after aspiration of gastric contents into the airway, or by stimulating an esophageal-bronchial neural cough reflex. Most studies define chronic a cough lasting more than 8 weeks [4].

LPR results from reflux of gastric contents beyond the upper esophageal sphincter and onto the tissues of the laryngopharynx, triggering chronic laryngitis or laryngopharyngitis. As in chronic laryngopharyngitis caused by other insults, patients often complain of chronic throat clearing, globus sensation, cough, throat pain, and/or vocal changes, especially hoarseness [5].

Asthma due to reflux might be induced by reflux of gastric contents into the tracheobronchial tree, causing direct irritation and bronchoconstriction. Alternatively, it might be caused by reflux of gastric contents into the esophagus, activating a neural reflex arc through the vagus nerve that leads to bronchoconstriction. As with asthma due to other causes, patients typically complain of wheezing and/or shortness of breath [6].

Patients presenting with extraesophageal manifestations of GERD often present without typical GERD symptoms (heartburn and regurgitation), which challenges the clinician's ability to identify the cause of the patient's complaint and risks misdiagnosis.

Diagnosis

Cough

There is no gold standard for diagnosing cough due to reflux [7]. However, investigators have used different methods to link chronic cough to reflux. Empiric therapy with antisecretory drugs over 8–16 weeks has been the traditional method used to distinguish cough due to reflux [8, 9]. Recurrence of cough upon discontinuation of therapy has also been used for diagnosis [10]. These diagnostic modalities have some drawbacks. First, antisecretory therapy may allow pharyngolaryngeal tissues to heal and resist activation of the cough reflex despite ongoing reflux. Second, the placebo effect in all related trials is large and variable. In fact, in RCTs that included a placebo arm, outcomes improved 1–34% in the placebo groups, and these improvements often met statistical significance [11, 12]. Other diagnostic have included: pathological reflux discovered with esophageal pH-monitoring or combined multichannel intraluminal impedance and pH (MII-pH) monitoring, esophageal dysmotility on esophageal manometry, or erosive esophagitis on esophagoscopy in patients with chronic cough [8, 13, 14]. However, the finding of abnormal esophageal acid exposure in a patient with chronic cough does not necessarily indicate that the cough is due to reflux. Therefore, to study the association and draw inferences on causality between chronic cough and reflux, investigators have evaluated combining esophageal (or pharyngoesophageal) pH-monitoring and MII-pH monitoring - a technique that can detect non-acid reflux – with a method of statistical analysis known as symptom association probability (SAP). SAP analysis consists in conducting a Fisher's exact test of association between reflux events (measured by the intraluminal pH or MII-pH monitor) and cough (which is usually self-reported). If a cough event is recorded within 2 min of a reflux event, then the two are considered associated and the Fisher's exact test for association between cough and reflux may confirm their association. SAP has been shown to be more sensitive to detect cough due to reflux than other indexes, such as the symptom index and symptom sensitivity index [14, 15]. Positive SAP on esophageal pH monitoring showed in one study to be the only statistically significant predictor of response to antisecretory therapy, with a sensitivity, specificity, positive predictive value,

and negative predictive value of 0.47, 0.82, 0.28 and 0.72, respectively [16]. Using MII-pH monitoring, another study showed that those with chronic cough without typical GERD symptoms and normal pH monitoring were SAP positive 44% of the time, 75% of which from non-acidic or weakly acidic reflux [7].

Attempts to prove a statistical association between cough episodes and esophageal reflux episodes in order to distinguish cough due to reflux has been complicated by the way cough is recorded. Patients record their symptoms using a symptom button on a monitoring device and/or in a symptom diary, so recording delays might be substantial. In fact, when patient reporting and concurrent recording of cough bursts on esophageal manometry are examined concurrently, Sifrim et al. demonstrated that only 39% of cough bursts recorded by manometry were reported by patients, and with an average delay of 28 s [7]. These delays and lost data might increase the false-negative rate of SAP testing.

Laryngopharyngeal Reflux

The diagnosis of LPR is equally challenging. Patients who present with symptoms of laryngitis, in whom other common causes, such as smoking, alcohol, industrial exposures, or chronic cough, have been ruled out, are usually started on an empiric trial of PPIs. If symptoms fail to resolve after 8–12 weeks, one might consider the possibility of LPR caused by non- or weakly acidic reflux, or other organic or functional disorders.

As for cough, there is no gold standard for diagnosing LPR. Diagnostic test include the response to antisecretory therapy, which is limited by a 40% placebo effect. Nevertheless, introducing the Reflux Symptom Index and the Reflux Finding Score (which incorporate symptoms of LPR and GERD) into clinical diagnosis has improved the diagnostic yield by 16–32% in the placebo arms of randomized controlled trials [17–19]. Esophageal and oropharyngeal pH monitoring have also been used as a diagnostic tool. However, their use is problematic because of the unclear role of non-acid or weakly acidic refluxate on pharyngolaryngeal tissues [20–22]. In addition to these methods, symptoms suggesting LPR, the finding of laryngitis on laryngoscopy, and the presence of esophagitis on endoscopy or in esophageal mucosal biopsies have been used to diagnose LPR [21, 23]. This methodology is potentially too restrictive, as patients without esophagitis may still have laryngitis caused by reflux as the tissues of the larynx may not be as resilient as the esophagus to exposure to gastric contents. By using these reference standards, many patients with LPR would be classified as not having LPR and the negative impacts on the specificity and the positive predictive value of the diagnostic tests might be significant.

Asthma

The diagnosis of asthma due to reflux is complicated by the nonspecific nature of the presenting complaints and the lack of a standard diagnostic test. Two methods have been used to link asthma to reflux: the presence of symptoms of asthma in those with GERD on esophageal pH monitoring [24], and the response of symptoms of asthma and/or pulmonary function tests to antisecretory therapy [25]. These reference standards might have excluded those with non- or weakly acid reflux as not having asthma due to reflux.

Treatment

Cough

Four randomized controlled trials have found no significant difference between proton-pump-inhibitors (PPI) and placebo groups in relieving cough due to reflux [11, 12, 26, 27] (Table 5.1). However, we point out that a large numbers of patients who might not have had cough due to

Table 5.1 Randomized trials on medical management of extraesophageal manifestations of GERD

Source	Sample size	Intervention	Primary outcomes	Main findings	P-value
Cough					
Shaheen 2011	40	Esomeprazole 40 mg bid for 12 weeks versus placebo	Change in Cough Specific Quality of Life Questionnaire score (CSQLQ)	Mean improvement in CSQLQ of 9.8 and 5.9 in treatment versus placebo group.	0.3
				Mean improvement in Fisman Cough Severity score of 1.0 vs. 0.8	0.7
				Mean improvement in Fisman Cough Frequency score of 3.2 vs. 2.3	0.3
Faruqi 2011	49	Esomeprazole 20 mg bid for 8 weeks	Change in integral response score for cough, change in Leicester Cough Questionnaire, change in Hull Airway Reflux Questionnaire, Reflux Finding Score (RFS), citric acid cough challenge	Change in cough frequency was 1.6 vs. 1.5	0.92
				Change in cough severity was 1.2 vs. 1.7	0.8
				Change in the Leicester Cough Questionnaire was 2.6 vs. 0.7	0.25
				Change in the RFS was 0.72 vs. 2.4	0.94
				Change in the Hull Airway Reflux Questionnaire was 7.3 vs. 7.1	0.61
				Change in log of inhaled citric acid concentration to produce 2 coughs was −0.15 vs. −0.04	0.66
				Change in log of inhaled citric acid concentration to produce 5 coughs was 0.02 vs. −0.09	0.57
Baldi 2006	35	Lansoprazole 30 mg qd and placebo dose in PM (control) versus lansoprazole 30 mg bid for 12 weeks.	Changes in cough scoring system and Visual Analog Scale (VAS)	Median change in VAS was 1.0 in both the treatment and control groups.	> 0.05
				Median change in cough scoring system was 1.0 vs. 0.5	> 0.05
				59% vs. 61% of patients had complete resolution of their symptoms.	> 0.05
Kiljander 2000	21	Omeprazole 40 mg qd for 8 weeks	Changes in cough symptom score	Cough symptom score −1.5 vs. +0.7	< 0.05
LPR					
Lam 2010	82	Rabeprazole 20 mg bid for 12 weeks	Change in Reflux Score Index (RSI) and RFS	At week 12, RSI −2.8 vs. +0.93	0.002
				At week 12, RFS −2.21 vs. −2.75	0.017
				At week 18, RSI −0.9 vs. + 0.58	0.12
				At week 18, RFS −3.2 vs. −3	0.68
McGlashan 2009	45	10 mL liquid dose of sodium alginate 1000 mg and potassium bicarbonate 200 mg after meals and at bedtime	Change in RSI and RFS from baseline at 2 month and 6 month follow up	At 2 months, RSI −12.7 vs. −7.8	0.005
				At 6 months, RSI −12.7 vs. −6.3	0.008
				At 2 months, RFS −2.2 vs. −0.6	0.08
				At 6 months, RFS −3.2 vs. −0.7	0.005

Table 5.1 (continued)

Source	Sample size	Intervention	Primary outcomes	Main findings	P-value
Reichel 2008	58	Esomeprazole 20 mg bid for 3 months	Change in RSI and RFS at 6 weeks and 3 months follow up, and subjective report of being symptom-free at 3 months.	At 6 weeks, RSI −9.87 vs. −6.93	NS
				At 3 months, RSI −14.27 vs. −7.79	< 0.05
				At 6 weeks, RFS −3.47 vs. −2.46	NS
				At 3 months, RFS −4.6 vs. −2.32	< 0.05
				At 3 months, 78.6% vs. 42.3% patients reported being symptom-free.	0.006
Wo 2006	35	Pantoprazole 40 mg daily for 12 weeks	Change in RFS, and subjective "adequate relief" of laryngeal symptoms.	Median RFS −1.0 vs. −3.0	NS
				Adequate relief of laryngeal symptoms was reported by 40% vs. 42% of patients	0.89
Vaezi 2006	145	Esomeprazole 40 mg bid for 16 weeks	Resolution of primary symptom, change in chronic posterior laryngitis index, and change in LPR-HRQL score.	Resolution of primary symptom was reported in 14.7% vs. 16% of patients	0.799
				CPLI −1.6 vs. −2.0	0.446
				LPR-HRQL score −11.6 vs. −7.8	0.424
Steward 2004	37	Rapeprazole 20 mg bid for 8 weeks	Change in reflux symptom score, subjective report of "significant global improvement", change in laryngeal grading of video-recorded strobe-laryngoscopy signs scoring system	Mean reflux symptom score −9.7vs. -6.6	0.44
				Significant global improvement was reported in 53.3% vs. 50% of patients.	1
				Laryngoscopic grade +0.6 vs. +0.5	0.69
Ehrer 2003	14	Pantoprazole 40 mg bid for 3 months (Placebo-controlled case-crossover trial)	Change in symptom score, change in laryngoscopic signs score	No statistically significant difference in mean symptom scores between groups (values unreported).	NS
				Mean laryngoscopic signs score −8.0 vs. −5.6 in the placebo-first group.	NS
Noordzij 2001	30	Omeprazole 40 mg bid for 8 weeks	Change in symptom score, change in laryngoscopic scores for vocal fold edema, arytenoid erythema, arytenoid edema, interarytenoid irregularity, and mucus accumulation.	Laryngeal symptom score −1078.6 vs. 1944.9	0.098
				No significant difference was found in the change in laryngoscopic sign scores.	NS
El-Serag 2001	20	Lansoprazole 30 mg bid for 3 months	Resolution of all presenting laryngeal symptoms, complete or partial resolution of all presenting laryngoscopic signs	Resolution of all presenting laryngeal symptoms was reported in 55% vs. 11% of patients	0.04
				Complete or partial resolution of laryngeal signs was found in 58% vs. 30% of patients	0.123

(continued)

Table 5.1 (continued)

Source	Sample size	Intervention	Primary outcomes	Main findings	P-value
Asthma					
Kiljander 2010	828	Three randomization groups: esomeprazole 40 mg daily and placebo daily, esomeprazole 40 mg bid, or placebo bid for 26 weeks	Changes in lung function tests, change in asthma quality of life questionnaire score, and experiencing a severe asthma exacerbation	Mean morning PEF improved +3.5 L and +5.5 L more in patients receiving esomeprazole daily and bid, respectively, compared to placebo.	NS
				Mean FEV1 improved 0.07 L more in patients receiving esomeprazole bid compared to placebo.	<0.0042
				Esomeprazole once daily was not statistically significantly better than placebo.	NS
				Mean AQLQ score increased 0.2 in patients receiving esomeprazole 40 mg daily, 0.3 in patients receiving esomeprazole bid, and 0.1 in patients receiving placebo.	< 0.001
				Severe asthma exacerbations experienced by 10%, 7.5%, and 10% of patients on esomeprazole once daily, bid, and placebo, respectively.	NS
Peterson 2009	30	Three randomization groups: rabeprazole 20 mg daily and placebo daily, rabeprazole 20 mg bid, or placebo bid	Subjective determination by subjects of improved exercise symptoms, changes in pulmonary function test, spirometry, SF-36 score, and mini-AQLQ score	Subjectively improved exercise tolerance was reported by 70% vs. 25% in patients on rabeprazole	0.03
				No statistically significant difference in change in FEV1, FVC, or FEV1/FVC between the rabeprazole groups and placebo.	NS
				There were no statistically significant difference in change in SF-36 or mini-AQLQ scores.	NS
Mastronarde 2009	393	Esomeprazole 40 mg bid	Rate of episodes of poor asthma control, change in PFTs, asthma symptoms, or asthma control	No. of episodes of poor asthma control per person-year was 2.5 vs. 2.3	0.66
				Change in FEV1 was 0 L vs. −0.02 L	0.36
				Change in FVC was 0 vs. −0.03	0.3
				Change in PEF was 9.2 L/min vs. 3.2 L/min	0.24
				Change in PC20 was 0.3 mg/mL vs. 1.5 mg/mL	0.04
				Change in JACQ, ASUI, mini-AQLQ, and SF-36 scores were not statistically significantly different between the treatment and placebo groups.	0.11–0.56

Table 5.1 (continued)

Source	Sample size	Intervention	Primary outcomes	Main findings	P-value
Sharma 2007	198	Omeprazole 20 mg bid and domperidone 10 mg tid for 16 weeks	Changes in asthma symptom score, rescue albuterol use, daytime and nighttime PEF, post-bronchodilator FEV1, and FVC	Daytime asthma symptom score decreased −0.48 vs. −0.22.	0.0001
				Nighttime asthma score decreased −0.51 vs. −0.14	0.0001
				Rescue albuterol puffs/week decreased −0.76 vs. −0.1	<0.0001
				Morning PEF increased +22.78 L/min vs. −0.76 L/min	<0.004
				Evening PEF increased +27.76 L/min vs. −1.43 L/min	0.002
				FEV1 increased +0.21 L vs. +0.07 L	0.0013
				FVC increased +0.18 L vs. −0.03 L	0.0023
Kiljander 2006	624	Esomeprazole 40 mg bid for 16 weeks	Change in morning and evening PEF	Morning PEF increased +22.3 L/min vs. +16 L/min in the last 28d of the study.	0.061
				Morning PEF increased +5.6 L/min more in the treatment group than in the placebo group after treatment was completed.	0.042
				In patients with GERD and nocturnal respiratory symptoms, morning PEF increased +8.7 L/min more in the treatment than the placebo group.	0.03
				Evening PEF increased +5.9 L/min more in the treatment group than in the placebo group.	0.053
				In patients with GERD and nocturnal respiratory symptoms evening PEF increased +11.2 L/min more in the treatment group than in placebo group.	0.02
Littner 2005	173	Lansoprazole 30 mg bid for 24 weeks	24-week average of asthma symptom score calculated from patient diaries, albuterol use, changes in PEF, post-bronchodilator FVC and FEV1, AQLQ score, and asthma exacerbations.	Asthma symptom scores decreased −0.36 vs. −0.21 in the placebo group.	NS
				Morning PEF increased +5 L/min vs. +10 L/min	NS
				Evening PEF increased +4 L/min vs. +12 L/min in the placebo group.	< 0.05
				Post-bronchodilator FEV1 changed 0 L in both groups.	NS
				Post-bronchodilator FVC changed 0 L vs. −0.1 L in the placebo group.	NS
				AQLQ score +0.9 vs. +0.7	< 0.05
				Albuterol use decreased 1 puff/day vs. −0.9 puffs per day	NS
				Asthma exacerbations were experienced by 8.1% vs. 20.4% of patients	0.017
				Moderate or severe asthma exacerbations were experienced by 4% vs. 13.9% of patients	0.016

(continued)

Table 5.1 (continued)

Source	Sample size	Intervention	Primary outcomes	Main findings	P-value
Sontag 2003	Total: 62 Control: 24 Medical: 22 Surgical: 16	Three randomization groups: lifestyle modifications and prn medications only (control), lifestyle modifications and ranitidine 150 mg tid, and lifestyle modifications and Nissen fundoplication, followed for 2 years	Change in asthma symptom score, requirement for pulmonary medications, and overall clinical response	Mean asthma symptom score improved significantly in 75% of surgical patients, 20% of control patients, and 0% of medical treatment patients.	0.008 (surgery vs. control and med. Groups combined)
				Need for rescue pulmonary medications decreased in 9.1% of patients in the medical group but increased in 18.2% of control patients. Pulmonary medication requirement decreased in 50% of patients in the surgical group. Zero patients in the control group changed their need for pulmonary medications.	NS
				Overall improvement occurred in 9.1% of medical, 75% of surgical, and 4.2% of control patients.	< 0.001 (surgery versus control and medical groups)
Jiang 2003	30	Two randomization arms: asthma treatment only versus asthma treatment plus omeprazole 20 mg qd, and domperidone 10 mg tid, for 6 weeks	Change in PFTs and histamine-induced bronchial sensitivity.	FVC increased +0.8 L vs. −0.2 L	< 0.05
				FEV1 increased +0.6 L vs. +0.1 L	< 0.05
				PEF increased +1.3 L/s vs. + 0.4 L/s	< 0.05
				Bronchial sensitivity improved +0.51 g/L vs. −0.03 g/L	< 0.05

reflux might have been enrolled in these trials, biasing the trials toward type II error. In addition, inclusion and exclusion criteria and outcomes varied between studies, making comparisons and meta-analysis difficult and inconclusive.

The surgical treatment of cough due to reflux is hampered by many of the same problems discussed for medical therapy and the difficulty of performing blinded, placebo-controlled trials. Observational studies varied in patient selection and the definition of outcomes measured [28–36]. With these limitations, most studies reported success rates of 65–74% [30, 32, 37, 38]. Patients who are more likely to report resolution of symptoms are those with concomitant typical GERD symptoms or positive esophageal pH monitoring [39]. The use of MII-pH monitoring in patients on bid PPI therapy has been limited but has shown that in patients with a positive non-acid symptom index for cough, antireflux surgery can achieve complete resolution of cough [40].

Laryngopharyngeal Reflux

Nine randomized trials have evaluated the efficacy of antisecretory therapy, primarily twice-daily PPIs, on LPR. These studies were relatively small, ranging in sample size from 14 to 145 subjects, and enrolled patients based on a varied combination of symptoms and laryngoscopic findings (Table 5.1). Six trials found no difference between treatment and placebo groups [17, 19, 41–44], whereas three trials reported statistically significant results [18, 45, 46]. Again, the difference in results might be explained by the placebo effect and the varied patient inclusion criteria.

No randomized controlled trials have compared medical and surgical intervention for LPR and only few small observational studies have been published [31, 47]. It is important to note that, as with other extraesophageal manifestation of GERD, patients who are more likely to report

resolution of symptoms (up to 72% of cases) are those with concomitant typical GERD symptoms and positive esophageal pH monitoring [47, 48].

Asthma

Nine randomized trials evaluated the effect of medical treatment of GERD on asthma due to reflux. Six randomized trials enrolled patients based on some combination of asthma and GERD [49–54]. Most studies reported changes in self-reported asthma symptoms and/or asthma-related quality of life indexes [49–53, 55, 56], and some reported differences in rescue bronchodilator use [49, 50, 52, 53] or in unscheduled healthcare visits for asthma [50, 56] (Table 5.1).

Among the three randomized trials that enrolled patients with both asthma and GERD, all reported greater improvement in the treatment than the placebo (or no treatment) groups. However, the differences in outcomes varied. Kiljander et al. found significant improvement in morning PEF, FEV_1, and the Asthma Quality of Life Questionnaire in subjects treated with esomeprazole 40 mg QD or BID compared to placebo. However they found no difference in changes in evening PEF, time to asthma exacerbation, number of severe asthma exacerbations, use of rescue inhalers, or asthma-free days [49]. Sharma et al. found greater improvement in mean daytime asthma symptom scores, mean nighttime asthma symptom scores, rescue inhaler use, morning PEF, evening PEF, FEV_1, and FVC in subjects treated with omeprazole 20 mg BID and domperidone 10 mg TID for 16 weeks compared to placebo [50]. Littner et al. found no significant differences in changes in diary-recorded asthma symptoms, rescue inhaler use, morning or evening PEF, FEV_1, FVC, or the Standardized Asthma Quality of Life Questionnaire score. However, they found significantly fewer patients in the treatment group experienced an asthma exacerbation or a moderate-severe asthma exacerbation [52].

The differences in outcomes between these trials may be explained by patient selection, both in terms of the severity of asthma and the severity of reflux in the study subjects. None of these trials utilized MII-pH monitoring to assess for non-acid esophageal reflux, and only one study enrolled patients with clinically silent GERD discovered on esophageal pH monitoring.

Only one trial randomized patients with both asthma and GERD (on pH monitoring and esophagitis on endoscopy) to medical or surgical treatment. After 2 years of follow-up, mean asthma symptom scores decreased more in the surgical group than in the medical group. Furthermore, 75% of surgical patients improved, markedly improved, or were cured of asthma when compared to 9% of the medical group. However changes in mean PEF, mean PEF percentage variation, PFTs, or asthma medication requirements were not significantly different [53].

Current Guidelines

Cough

The American College of Chest Physicians (ACCP) guidelines define chronic a cough lasting 8 weeks or longer. In patients who do not smoke and do not take an ACE inhibitor, ACCP recommends to evaluate for upper airway cough syndrome (UACS, also known as post-nasal drip syndrome), asthma, non-asthmatic eosinophilic bronchitis (NAEB), and GERD – the most common causes of chronic cough. Patients with chronic cough and typical symptoms of GERD, or patients whose chronic cough persists after ruling out or treating UACS, asthma, and NAEB should undergo medical treatment for GERD – dietary and lifestyle modifications with acid suppression therapy, and prokinetic therapy if there is no response to the initial therapy. Response should be assessed 1–3 months after initiation of therapy. Patients with typical symptoms of GERD whose cough does not resolve with antisecretory therapy should undergo esophageal pH monitoring while on therapy to determine if antisecretory therapy has failed. Maximal medical therapy includes an antireflux diet (<45 g of fat per day, elimination of coffee, tea, soda, chocolate, mints, citrus, and alcohol), eliminating smoking, and limiting activities that increase intraabdominal pressure, maximal PPI therapy, and prokinetic therapy. Antireflux surgery is recommended in patients who have positive esophageal pH monitoring, in whom cough has not

improved after a minimum of 3 months of maximal medical therapy, and in whom reflux is present while on maximal medical therapy. The ACCP guidelines do not address the diagnostic role of MII-pH monitoring or association tests, and they state that esophageal pH monitoring is the most sensitive and specific test for cough due to reflux [4, 57, 58]. However, more recent data support using combined MII-pH monitoring with SAP analysis while continuing medical therapy when patients fail to respond to antisecretory therapy, instead of using pH monitoring alone. Furthermore, more recent data might support using in selected patients concomitant esophageal manometry to objectively record cough episodes instead of less reliable patient recordings. Finally, patients who have been ruled out or treated for the three other most common causes of chronic cough and in whom MII-pH monitoring shows acid or non-acid reflux while on maximal antisecretory therapy, might be considered for evaluation for antireflux surgery (Table 5.2).

Table 5.2 Level of recommendation for systematic review of recent literature compared to current practice guidelines for management of extraesophageal manifestations of GERD

		Recommendation	
Intervention	Current evidence review and guidelines	Level	Class
Cough			
Treating chronic cough with medical antisecretory therapy.		**A**	**IIb**
Evidence review	Randomized controlled trials on treating suspected cough due to reflux with PPIs have had mixed results. Shaheen 2011 (patients with chronic cough and without typical GERD symptoms) and Faruqi 2011 (patients with chronic cough and with or without typical GERD symptoms) showed no improvement in cough-related quality of life, cough severity, cough frequency, induced cough threshold compared to placebo. However, Kiljander 2000 (patients with chronic cough and abnormal esophageal pH monitoring) showed greater improvement in cough symptoms with omeprazole compared to placebo.		
Practice guidelines	Patients with persistent chronic cough, who do not smoke and are not taking an ACE inhibitor, after ruling out upper airway cough syndrome, asthma, and non-asthmatic eosinophilic bronchitis, should undergo medical treatment for GERD. (ACCP)		
Treating patients with chronic cough and typical symptoms of GERD with medical antisecretory therapy.		**B**	**IIb**
Evidence review	Two randomized controlled trials enrolled patients with chronic cough and a diagnosis of GERD. Baldi 2006 compared daily to twice-daily lansoprazole, and found that bid therapy was not significantly better than daily therapy. Kiljander 2000 showed greater improvement in cough symptoms with omeprazole compared to placebo. While patients with typical symptoms of GERD should be treated, whether or not treating their GERD has a positive impact on their chronic cough is not clear.		
Practice guidelines	Patients with chronic cough and typical symptoms of GERD should undergo medical treatment for GERD (ACCP).		
Using esophageal monitoring to diagnose cough due to reflux.		**B**	**IIa**

Table 5.2 (continued)

		Recommendation	
Intervention	Current evidence review and guidelines	Level	Class
Evidence review	Studies evaluated the utility of esophageal monitoring – pH and MII-pH monitoring, on and off antisecretory therapy, with subjective and objective reporting of cough in diagnosing cough due to reflux. A prospective case-control study found that weakly acidic gas reflux was unique to patients with cough due to reflux compared to patients with GERD and healthy controls. (Kawamura 2011) Retrospective studies found esophageal pH monitoring with SAP analysis with self-reported cough off antisecretory therapy (Hersh 2010) had 26% of patients with cough due to reflux with a positive SI for non-acid reflux during esophageal MII-pH monitoring, and with self-reported cough on antisecretory therapy (Tutuian 2006). A prospective cohort study on esophageal MII-pH monitoring off antisecretory therapy with SAP analysis and cough recorded with concurrent manometry found 77% of patients with cough due to reflux were SAP positive, while 44% of patients without cough due to reflux were SAP positive. This study also reported that only 39% of cough bursts were not recorded by patients, and those that were recorded were delayed by 28 s. (Sifrim 2005) These studies were all small ($n \leq 61$) and some had significant methodological flaws.		
Practice guidelines	Patients with typical symptoms of GERD whose cough does not resolve with antisecretory therapy should undergo esophageal pH monitoring while on antisecretory therapy to determine whether medical therapy has failed (ACCP).		
Antireflux surgery for the treatment of cough due to reflux.		**B**	**IIb**
Evidence review	No randomized controlled trial has compared medical to surgical treatment of cough due to reflux in any patient population. Two prospective cohort studies have observed patients who underwent antireflux surgery after a negative workup for other causes of chronic cough. Allen 2004 reported on 79 patients who had a negative workup for UACS and asthma and complained primarily of respiratory symptoms before undergoing laparoscopic Nissen fundoplication. At 5-years follow-up patients subjectively reported 36% were cured of cough, 35% were improved, 24% were unchanged, and in 5% cough was worse. Brouwer in 2003 reported on 28 patients who underwent laparoscopic Nissen fundoplication for predominantly respiratory symptoms. Mean cough score decreased from 4.7 to 0.4 at mean 650 days follow-up. 19 patients had cough or "aspiration-type symptoms": 53% reported resolution of their symptoms (symptom score of 0/5), 32% had marked improvement (symptom score of 1/5), 11% reported some improvement, and 5% were unchanged.		
Practice guidelines	Antireflux surgery is recommended in patients who have positive esophageal pH monitoring in whom cough has not improved after a minimum of 3 months of maximal medical therapy and lifestyle modifications and esophageal monitoring studies show continued reflux while on maximal medical therapy (ACCP).		

(continued)

Table 5.2 (continued)

		Recommendation	
Intervention	Current evidence review and guidelines	Level	Class
LPR			
Use of the Reflux Symptom Index to diagnose LPR		**B**	**IIb**
Evidence review	One prospective study has evaluated the Reflux Symptom Index (Belafsky 2002). The authors reported mean RSI of patients with LPR was 19.9, and of healthy controls was 11.6. They considered RSI > 13 abnormal and indicative of LPR.		
Practice guidelines	Patients with suspected LPR should be evaluated with the Reflux Symptom Index and Reflux Finding Score. If > 13 and > 7, then patients should undergo an empiric trial of antisecretory therapy (Ford 2005).		
Use of the Reflux Finding Score to diagnose LPR		**B**	**IIb**
Evidence review	Belafsky 2001: mean RFS of patients with LPR was 11.5. Interrater reliability was 0.9.		
Practice guidelines	Patients with suspected LPR should be evaluated with the Reflux Symptom Index and Reflux Finding Score. If > 13 and > 7, then patients should undergo an empiric trial of antisecretory therapy (Ford 2005).		
Use of the Laryngoscopic Reflux Index score to diagnose LPR		**C**	**IIb**
Evidence review	Jonaitis 2006: LRI significantly higher in patients with LPR versus healthy controls. LRI > 5 significantly more common in cases than controls, but test characteristics unreported.		
Practice guidelines	Not addressed.		
Use of laryngoscopy to diagnose LPR		**B**	**IIa**
Evidence review	Three prospective studies have examined the use of laryngoscopy to diagnose LPR. In one case-control study (Vavricka 2007), only posterior pharyngeal wall cobblestoning was more common in cases than controls (66% vs 55%). Agreement between blinded observers on laryngeal findings ranged from good to poor. Another prospective study found that only interarytenoid mucosal inflammation and inflammation of the true vocal cords were significant predictors of response to antisecretory therapy (Park 2005). Another prospective study compared transnasal flexible fiberoptic laryngoscopy to transoral rigid laryngoscopy, finding fiberoptic laryngoscopy superior in detecting laryngeal findings.		
Practice guidelines	Laryngoscopic findings are highly suggestive of LPR: posterior laryngitis, contact granuloma, and pseudosulcus (Ford 2005).		
Esophageal pH or MII-pH monitoring to diagnose LPR		**B**	**IIb**
Evidence review	Two prospective studies have examined esophageal or pharyngoesophageal pH monitoring to diagnose LPR. One found increased laryngopharyngeal bolus exposure time and increased distal AET were only two significant predictors of response to PPI therapy (Wang 2012), while the other found that 52% of patients with laryngeal symptoms and 38% of patients with typical GERD symptoms had laryngopharyngeal acid reflux episodes during monitoring (Yorulamz 2003).		
Practice guidelines	In patients whose symptoms do not resolve after 6 months, or improve after 3 months, pharyngoesophageal MII-pH monitoring should be utilized to demonstrate reflux (Ford 2005).		

Table 5.2 (continued)

		Recommendation	
Intervention	Current evidence review and guidelines	Level	Class
Empiric PPI trial to diagnose LPR		**B**	**IIb**
Evidence review	One prospective trial examined the sensitivity and specificity of an empiric trial of twice daily PPIs to diagnose LPR, reporting positive and negative predictive values of 86% and 25%, respectively (Masaany 2011).		
Practice guidelines	If patients have RSI > 13 and RFS > 7, initiate 3–6 months of anti-reflux diet, lifestyle modifications, and twice daily PPI therapy.		
Treatment of LPR with PPIs		**A**	**IIb**
Evidence review	Eight randomized trials have compared twice daily PPI therapy with placebo. Some followed changes in the RSI and RFS. Six of these trials reported no differences between the placebo and treatment groups while 2 did report significant differences. Reichel 2008 showed RSI and RFS both improved at 3 months in patients treated with esomeprazole 20 mg bid, while El-Serag 2001 reported a greater percentage of patients in the treatment group reporting complete resolution of their symptoms than in the placebo group (55% vs 11%), but no difference in change in laryngeal signs of inflammation between the two groups (Lam 2010, Reichel 2008, Wo 2006, Vaezi 2006, Steward 2004, Ehrer 2003, Noordzij 2001, El-Serag 2001).		
Practice guidelines	Recommends treating patients with 3–6 months of twice daily PPI therapy.		
Treatment of LPR with sodium alginate and potassium bicarbonate.		**B**	**IIa**
Evidence review	One randomized non-placebo controlled trial has evaluated the effect of treating LPR with sodium alginate and potassium bicarbonate found RSI and RFS improved significantly from baseline to 2 months (RSI only) and baseline to 6 months (RSI and RFS) (McGlashan 2009).		
Practice guidelines	Not addressed.		
Antireflux surgery for LPR		**C**	**IIb**
Evidence review	No randomized trials have compared medical to surgical therapy for LPR. Swoger 2006 reported a prospective cohort of 25 patients who were unresponsive to PPI therapy. 10 chose to have surgery. At 1 year follow up, 1 patient in the surgery group and 1 patient in the medical groups reported resolved symptoms.		
Practice guidelines	In patients whose pharyngoesophageal MII-pH monitoring demonstrates reflux, referral should be made for surgery.		
Asthma			
Use of esophageal acidification to diagnose asthma due to reflux		**C**	**IIb**
Evidence review	One prospective case-control study used an increase of 100 μg in PD_{20} FEV_1 of a methacholine inhalation test after esophageal acidification to diagnose asthma due to reflux. Positive and negative predictive values were reported as 86% and 82%, respectively. (Dal Negro 2009)		
Practice guidelines	Not addressed		

(continued)

Table 5.2 (continued)

		Recommendation	
Intervention	Current evidence review and guidelines	Level	Class
Use of esophageal pH monitoring to diagnose asthma due to reflux		**B**	**IIb**
Evidence review	One randomized case-crossover trial (Kiljander 2001) studied esophageal pH monitoring to diagnose asthma due to reflux. The authors found that mean distal esophageal acid exposure time (11% vs 8%) and supine distal esophageal acid exposure time (12% vs 8%) were statistically significantly higher in patients whose asthma responded to therapy with omeprazole than in patients whose asthma did not respond to omeprazole.		
Practice guidelines	The Expert Panel recommends that patients with poorly controlled asthma despite maximal medical therapy should be evaluated for GERD with esophageal pH monitoring. (NIH-EPR3)		
Use of antisecretory therapy in patients with typical GERD symptoms and asthma		**A**	**I**
Evidence review	Three placebo-controlled randomized trials and 1 uncontrolled randomized trial have evaluated the effect of twice daily PPI therapy on asthma symptoms and pulmonary function tests in patients with GERD. Three (Kiljander 2010, Sharma 2007, Jiang 2003) found improvement in PFTs, while 1 (Littler 2005) did not.		
Practice guidelines	The Expert Panel recommended that patients with asthma and GERD symptoms should be treated for GERD. (NIH-EPR3).		
Use of antisecretory therapy in patients without typical GERD symptoms but with positive pH monitoring and asthma.		**B**	**IIb**
Evidence review	One randomized trial evaluated the effect of twice-daily PPI therapy on asthma symptoms in patients without typical GERD symptoms. Mastronarde 2009 found no difference in episodes of poor asthma control, PFTs, or asthma symptoms in patients without typical GERD symptoms, including patients with silent GERD discovered on esophageal pH monitoring.		
Practice guidelines	Not addressed.		
Antireflux surgery for asthma due to reflux.		**B**	**IIb**
Evidence review	One randomized controlled trial compared antireflux surgery to H2 blocker therapy for asthma due to reflux (Sontag 2003). It found that at 2 years asthma symptom scores decreased significantly more in the surgical group than in the H2 blocker and placebo groups combined. 75% of surgical patients had improvement, marked improvement, or cure of asthma after 2 years follow up. However pulmonary function tests and asthma medication requirements were not significantly different between the groups. Rakita 2006 found mean asthma symptom scores decreased from 4.7 to 1.7 after antireflux surgery (laparoscopic Nissen fundoplication) in patients who presented with a mean asthma symptom score of at least 4.		
Practice guidelines	Surgical treatment has been reported to reduce the symptoms of asthma and medication requirements (NIH-EPR3)		

Laryngopharyngeal Reflux

The American Academy of Otolaryngology published guidelines on hoarseness in 2009 [59]. Ford published a review of the available evidence in 2005. He recommended evaluating patients with suspected LPR with both the Reflux Symptom Index and the Reflux Finding Score. If greater than 13 and 7, respectively, he recommended proceeding to treatment with 3–6 months of an antireflux diet, lifestyle modifications (quitting smoking and alcohol intake), and twice daily PPI therapy. He recommended titrating medications off in patients whose symptoms resolved after 3 or 6 months. If symptoms improved but did not resolve after 6 months, or if symptoms did not improve at all after 3 months, Ford recommended evaluation with MII-pH monitoring to demonstrate reflux, and esophageal manometry and endoscopy to guide possible operative planning [5]. More recent data support supports prescribing 8–12 weeks of twice-daily PPIs and reevaluation in patients in whom LPR is suspected and in whom other common causes of chronic laryngitis have been ruled out. Similarly, evaluation for antireflux surgery should include extensive counseling about the uncertainty of outcomes, and patients with objective evidence of GERD should be offered surgery with the understanding that resolution of extraesophageal symptoms is less reliable than those of typical symptoms.

Asthma

The National Heart, Lung, and Blood Institute of the National Institutes of Health released its Expert Panel Report 3 in 2007, with guidelines for the diagnosis and management of asthma [6]. These guidelines recommend that clinicians should evaluate patients with asthma for GERD when asthma is poorly controlled on maximal medical therapy. The panel recommended that patients with concomitant GERD symptoms should be treated for GERD, while patients with poorly controlled asthma despite maximal medical therapy should undergo evaluation for GERD even in the absence of typical GERD symptoms. The panel noted that antireflux surgery has been reported to reduce asthma symptoms and medication requirements, but did not explicitly endorse antireflux surgery as a means of controlling asthma due to reflux. The guidelines do not specifically address how to diagnose asthma due to reflux.

Recent evidence provides further support for the role of GERD in patients with uncontrolled asthma. Given the morbidity and mortality associated with uncontrolled asthma it is reasonable to initiate antisecretory therapy on an empiric basis in patients with uncontrolled asthma without definitive proof of pathologic reflux. In patients who do not respond to maximal antisecretory therapy and appropriate asthma therapy it might be reasonable to resort to MII-pH monitoring while on antisecretory therapy. It may be reasonable to refer patients for antireflux surgery, however as in the case of LPR, antireflux surgery is largely an unproven therapy for asthma due to reflux. Patients should be extensively counseled about the unknown likelihood of benefit before referral for surgery, and should only be offered an operation if their asthma is accompanied by objective evidence of GERD, an event that can increase the likelihood of a successful operation.

Conclusions

Extraesophageal manifestations of reflux are estimated to cost $50 billion in healthcare expenditures annually and are responsible for 12.9% of all primary care provider encounters, yet they remain difficult to diagnose and treat. Extraesophageal manifestations of reflux may be most effectively diagnosed with a stepwise approach incorporating empiric treatment with antisecretory therapy, combined MII-pH monitoring, and surgical intervention in highly selected cases.

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References

1. Rubenstein JH, Chen JW. Epidemiology of gastroesophageal reflux disease. Gastroenterol Clin North Am. 2014;43(1):1–14.
2. Francis DO et al. High economic burden of caring for patients with suspected extraesophageal reflux. Am J Gastroenterol. 2013;108(6):905–11.
3. Schappert S, Burt C. Ambulatory care visits to physican offices, hospital outpatient departments, and emergency departments: United States, 2001–02. Vital and Health Statistics. 2006, Natinal Center for Health Statistics.
4. Irwin RS. Chronic cough due to gastroesophageal reflux disease : Accp evidence-based clinical practice guidelines. Chest. 2006;129(1_suppl):80S–94S.
5. Ford CN. Evaluation and management of laryngopharyngeal reflux. Jama. 2005;294(12):1534–40.
6. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma-summary report 2007. J Allergy Clin Immunol. 2007;120(5 Suppl):S94–138.
7. Sifrim D et al. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. Gut. 2005;54(4):449–54.
8. Xu X et al. Comparison of gastroesophageal reflux disease questionnaire and multichannel intraluminal impedance pH monitoring in identifying patients with chronic cough responsive to antireflux therapy. Chest. 2014;145(6):1264–70.
9. Ojoo JC et al. Management of patients with chronic cough using a clinical protocol: a prospective observational study. Cough. 2013;9(1):2.
10. Kawamura O et al. Increase of weakly acidic gas esophagopharyngeal reflux (EPR) and swallowing-induced acidic/weakly acidic EPR in patients with chronic cough responding to proton pump inhibitors. Neurogastroenterol Motil. 2011;23(5):411–8. e172.
11. Faruqi S et al. Chronic cough and esomeprazole: a double-blind placebo-controlled parallel study. Respirology. 2011;16(7):1150–6.
12. Shaheen NJ et al. Randomised clinical trial: high-dose acid suppression for chronic cough – a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2011;33:225–34.
13. Everett CF, Morice AH. Clinical history in gastroesophageal cough. Respir Med. 2007;101(2):345–8.
14. Avidan B et al. Temporal associations between coughing or wheezing and acid reflux in asthmatics. Gut. 2001;49(6):767–72.
15. Wunderlich AW, Murray JA. Temporal correlation between chronic cough and gastroesophageal reflux disease. Dig Dis Sci. 2003;48(6):1050–6.
16. Hersh MJ, Sayuk GS, Gyawali CP. Long-term therapeutic outcome of patients undergoing ambulatory pH monitoring for chronic unexplained cough. J Clin Gastroenterol. 2010;44(4):254–60.
17. Lam PK et al. Rabeprazole is effective in treating laryngopharyngeal reflux in a randomized placebo-controlled trial. Clin Gastroenterol Hepatol. 2010;8(9):770–6.
18. Reichel O et al. Double-blind, placebo-controlled trial with esomeprazole for symptoms and signs associated with laryngopharyngeal reflux. Otolaryngol Head Neck Surg. 2008;139(3):414–20.
19. Wo JM et al. Double-blind, placebo-controlled trial with single-dose pantoprazole for laryngopharyngeal reflux. Am J Gastroenterol. 2006;101(9):1972–8.
20. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice. 2002;16(2):274–7.
21. Masaany M et al. Empirical treatment with pantoprazole as a diagnostic tool for symptomatic adult laryngopharyngeal reflux. J Laryngol Otol. 2011;125(5):502–8.
22. Ylitalo R, Lindestad P, Hertegard S. Pharyngeal and laryngeal symptoms and signs related to extraesophageal reflux in patients with heartburn in gastroenterology practice: a prospective study. Clin Otolaryngol. 2005;30(4):347–52.
23. Songur N et al. Gastroesophageal scintigraphy in the evaluation of adult patients with chronic cough due to gastroesophageal reflux disease. Nucl Med Commun. 2008;29(12):1066–72.
24. Dal Negro RW et al. A MCh test pre-post esophageal acidification in detecting GER-related asthma. J Asthma. 2009;46(4):351–5.
25. Kiljander T et al. Asthma and gastro-oesophageal reflux: can the response to anti-reflux therapy be predicted? Respir Med. 2001;95:387–92.
26. Baldi F et al. Proton pump inhibitor treatment of patients with gastroesophageal reflux-related chronic cough: a comparison between two different daily doses of lansoprazole. World J Gastroenterol WJG. 2006;12:82–8.
27. Kiljander TO et al. Chronic cough and gastro-oesophageal reflux: a double-blind placebo-controlled study with omeprazole. Eur Respir J. 2000;16(4):633–8.
28. Brown SR et al. Clinical outcomes of atypical extra-esophageal reflux symptoms following laparoscopic antireflux surgery. Surg Endosc. 2011;25(12):3852–8.
29. Hoppo T, Komatsu Y, Jobe BA. Antireflux surgery in patients with chronic cough and abnormal proximal exposure as measured by hypopharyngeal multichannel intraluminal impedance. JAMA Surg. 2013;148(7):608–15.
30. Kaufman JA et al. Long-term outcomes of laparoscopic antireflux surgery for gastroesophageal reflux disease (GERD)-related airway disorder. Surg Endosc. 2006;20(12):1824–30.
31. Koch OO et al. Effectiveness of laparoscopic total and partial fundoplication on extraesophageal manifestations of gastroesophageal reflux disease: a randomized study. Surg Laparosc Endosc Percutan Tech. 2012;22(5):387–91.

32. Rakita S et al. Laparoscopic Nissen fundoplication offers high patient satisfaction with relief of extra-esophageal symptoms of gastroesophageal reflux disease. Am Surg. 2006;72(3):207–12.
33. Ranson ME et al. Prospective study of laparoscopic nissen fundoplication in a community hospital and its effect on typical, atypical, and nonspecific gastrointestinal symptoms. Jsls. 2007;11(1):66–71.
34. van der Westhuizen L et al. Impact of Nissen fundoplication on laryngopharyngeal reflux symptoms. Am Surg. 2011;77(7):878–82.
35. Zhang C et al. A preliminary investigation of laparoscopic fundoplication treatment on gastroesophageal reflux disease-related respiratory symptoms. Surg Laparosc Endosc Percutan Tech. 2012;22(5):406–9.
36. Oelschlager BK, et al. Long-term outcomes after laparoscopic antireflux surgery. Am J Gastroenterol. 2008;103(2):280–7; quiz 288.
37. Iqbal M et al. Outcome of surgical fundoplication for extra-oesophageal symptoms of reflux. Surg Endosc. 2009;23(3):557–61.
38. Thoman DS et al. Laparoscopic antireflux surgery and its effect on cough in patients with gastroesophageal reflux disease. J Gastrointest Surg. 2002;6(1):17–21.
39. Francis DO et al. Traditional reflux parameters and not impedance monitoring predict outcome after fundoplication in extraesophageal reflux. Laryngoscope. 2011;121(9):1902–9.
40. Tutuian R et al. Nonacid reflux in patients with chronic cough on acid-suppressive therapy. Chest. 2006;130(2):386–91.
41. Eherer AJ et al. Effect of pantoprazole on the course of reflux-associated laryngitis: a placebo-controlled double-blind crossover study. Scandinavian journal of gastroenterology. 2003;38(5):462–7.
42. Noordzij JP et al. Evaluation of omeprazole in the treatment of reflux laryngitis: a prospective, placebo-controlled, randomized, double-blind study. Laryngoscope. 2001;111(12):2147–51.
43. Steward DL et al. Proton pump inhibitor therapy for chronic laryngo-pharyngitis: a randomized placebo-control trial. Otolaryngol Head Neck Surg. 2004;131(4):342–50.
44. Vaezi MF et al. Treatment of chronic posterior laryngitis with esomeprazole. Laryngoscope. 2006;116:254–60.
45. El-Serag HB et al. Lansoprazole treatment of patients with chronic idiopathic laryngitis: a placebo-controlled trial. Am J Gastroenterol. 2001;96(4):979–83.
46. McGlashan JA et al. The value of a liquid alginate suspension (Gaviscon Advance) in the management of laryngopharyngeal reflux. Eur Arch Otorhinolaryngol. 2009;266(2):243–51.
47. Swoger J et al. Surgical fundoplication in laryngopharyngeal reflux unresponsive to aggressive acid suppression: a controlled study. Clin Gastroenterol Hepatol. 2006;4(4):433–41.
48. Fernando HC, et al. Efficacy of laparoscopic fundoplication in controlling pulmonary symptoms associated with gastroesophageal reflux disease. Surgery. 2005;138(4): 612–6; discussion 616–7.
49. Kiljander TO et al. Effect of esomeprazole 40 mg once or twice daily on asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2010;181:1042–8.
50. Sharma B et al. Effect of omeprazole and domperidone on adult asthmatics with gastroesophageal reflux. World J Gastroenterol. 2007;13(11):1706–10.
51. Shimizu Y et al. A proton pump inhibitor, lansoprazole, ameliorates asthma symptoms in asthmatic patients with gastroesophageal reflux disease. Tohoku J Exp Med. 2006;209(3):181–9.
52. Littner MR et al. 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;128:1128–35.
53. Sontag SJ 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):987–99.
54. Jiang SP et al. Effects of antireflux treatment on bronchial hyper-responsiveness and lung function in asthmatic patients with gastroesophageal reflux disease. World J Gastroenterol. 2003;9(5):1123–5.
55. Peterson KA et al. The role of gastroesophageal reflux in exercise-triggered asthma: a randomized controlled trial. Dig Dis Sci. 2009;54:564–71.
56. Mastronarde JG et al. Efficacy of esomeprazole for treatment of poorly controlled asthma. N Engl J Med. 2009;360:1487–99.
57. Irwin RS et al. Diagnosis and management of cough executive summary : Accp evidence-based clinical practice guidelines. Chest. 2006;129(1_Suppl):1S–23S.
58. Pratter MR et al. An empiric integrative approach to the management of cough: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):222S–31S.
59. Schwartz SR et al. Clinical practice guideline: hoarseness (dysphonia). Otolaryngol Head Neck Surg. 2009;141(3 Suppl 2):S1–31.