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GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Highlights from the Cleveland Clinic's 4th Bi-Annual Esophageal Summit

CONTROVERSIES: ASTHMA AND COUGH IN GERD PATIENTS—Joel E. Richter, MD, Professor of Medicine, and Chairman, Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland

Asthma: increased mucus secretion, edema in airways, bronchospasm; contributing factors include allergy, exercise, cold weather, and acid reflux; 30% to 90% of patients also have cough

Prevalence of GERD in asthmatics varies: 32% of 105 European asthmatics had abnormal 24-hr pH studies; although 50% of patients had no symptoms of classic GERD, approximately 33% had esophagitis; 82% of asthmatics in study at Veterans Affairs (VA) clinics had reflux, of whom approximately 40% had esophagitis (including Barrett's esophagus)

Possible mechanisms: acid material trickling into trachea may cause bronchospasm (microaspiration); upper gastrointestinal (GI) tract and respiratory tree derived from same embryonal ridge and therefore have vagal connections and similar protective mechanisms; Richter and colleagues tested hypothesis in healthy controls with no history of asthma or reflux, and in patients with reflux alone, asthma alone, or asthma and reflux; in all groups, acid exposure changed peak expiratory flow rate (PEFR); however, after rinse out, controls and patients with asthma alone recovered PEFR, but patients with asthma and GERD did not, and some worsened

Asthma as contributor to GERD: large amount of coughing and wheezing could change intraesophageal and intrathoracic pressures, leading to reflux in patients with weak lower esophageal sphincters (LES); some drugs used in treatment of asthma may cause decrease in LES pressure in some patients

Silent GERD: physician should have high index of suspicion for GERD in difficult-to-manage asthma; asthma patients may have GERD without exhibiting classic GERD symptoms; manometry and 24-hr pH monitoring show asthma patients with silent reflux have same amount of reflux as those with

reflux symptoms, but have higher LES pressure; study data show patients with silent reflux have more frequent episodes of acid reflux per hour and more acid exposure day and night

Proton pump inhibitors (PPIs): *omeprazole*—in speaker's study (not placebo controlled) of patients with both asthma and reflux, adequate acid control documented by 24-hr pH monitoring; at 3-mo follow-up, 22 responders (asthma improved) and 8 nonresponders; PEFr improved in responders but not in nonresponders; 75% of patients in study required only 20 mg of omeprazole; however, 60 mg insufficient in one patient; *lansoprazole*—among 207 asthma patients given placebo or lansoprazole 30 mg bid, lansoprazole improved quality of life, forced vital capacity, and evening PEFr, particularly in patients with difficult-to-manage asthma; however, results from other studies using large PPI doses equivocal; data may apply only to certain patients

Surgery: literature review found approximately 80% of asthma patients treated surgically improve clinically, and 88% require less medication postoperatively, but no evidence that pulmonary function tests improve; *surgery vs medical therapy*—2 clinical trials with 5-yr follow-up; Chilean trial suggested that H₂-blockers as effective as surgery; in US trial, after 5-yr follow-up, only surgical patients could reduce medication (H₂-blockers only); *observation*—if reflux minimal contributing factor to asthma, antireflux surgery or PPI will not help

Factors that suggest GERD as cause of cough: daytime nonproductive chronic cough, or onset after viral upper respiratory infection; pH monitoring inadequate to prove GERD cause of cough; esophageal and hypopharyngeal manometry of cough episodes determine if acid reflux precedes cough or if cough initiates reflux; diagnosis of GERD as cause of cough definitive only if cough resolves after antireflux therapy; most studies retrospective and not placebo controlled (all consistently show that medical or surgical treatment helpful; however, most did not use H₂-blocker, PPI, or prokinetic); *speaker's study*—placebo controlled; in nonasthmatic patients with persistent daily cough despite treatment for postnasal drip, reflux established by manometry and pH testing; randomized to omeprazole 40 mg bid or placebo for 12 wk; only 35% showed dramatic reduction in cough

Cost analysis: if physician highly suspicious that patient has acid reflux, initial therapeutic trial less expensive overall than testing first; if patient does well, taper dosage downward; if symptoms return, acid reflux confirmed; if patient does not improve during therapeutic trial, test patient while on medication, particularly if symptom constellation unusual

GERD TYPICALLY CAUSES THROAT CHANGES—Douglas M. Hicks, PhD, Director, The Voice Center, and Head, Speech-Language Pathology, Head and Neck Institute, the Cleveland Clinic, Cleveland

Introduction: GI specialists rely on objective tests, *eg*, 24-hr pH probes, and claim that ear, nose, and throat specialists overdiagnose reflux laryngitis based on symptoms (*eg*, burning throat) and signs (*eg*, tissue irritation and inflammation in hypopharynx and posterior larynx); clinically diagnosed symptoms resolve when patients treated with antireflux medication

Laryngopharyngeal reflux (LPR): manifests in larynx and hypopharynx; has atypical acid reflux profile different from that of GERD; data suggest that 50% of patients with LPR do not exhibit typical GERD symptom profile

Physical examination signs of LPR: interarytenoid bar or tissue band that spans posterior commissure, arytenoid cartilage towers (redness along medial wall of arytenoid complex streaking over superior surface of true vocal folds); erythema of vocal folds; edema bilaterally in vocal folds (unlike straight medial edges usually seen)

Studies in support of hypothesis that GERD causes laryngitis: *studies in dogs*—document that

pepsin and bile in acid environment causes laryngeal tissue damage seen histologically as inflammation; *clinical pH studies*—show that patients with atypical reflux experience more refluxate up to proximal esophageal level and hypopharynx; proximal-probe pattern different in LPR from that of GERD patients, and LPR patients have more proximal-probe exposure; hypopharyngeal probe profile also different; *reflux findings score (RFS)*—endoscopic examination rating score; indicates type and severity of laryngeal tissue irritation signs can differentiate patients with LPR profile from controls; *placebo-controlled GI study*—confirms cause-and-effect relationship between reflux symptom relief and antireflux medical management

MEDICAL TREATMENT—Gary W. Falk, MD, Director, Center for Swallowing and Esophageal Disorders, Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland

Goals of acute therapy: symptom relief, healing of erosions, and prevention of complications; goals of long-term therapy symptom relief and maintenance of healing; medical therapy may involve lifestyle changes and treatment with prokinetics, H₂-blockers, or PPIs

Does PPI treatment work? treatment relieves symptoms, heals erosions and ulcers, prevents complications (*ie*, strictures), maintains symptom control and healing; meta-analysis showed PPIs superior to H₂-blockers for healing erosive esophagitis; 80% of GERD patients with erosive esophagitis heal and achieve symptom relief within 12 wk on PPIs

Specific PPIs: omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole essentially equivalent therapeutically; esomeprazole may be superior to omeprazole only for grades C and D esophagitis; 50% to 60% of patients with symptomatic acid reflux have normal endoscopic examination or small hiatal hernia; *endoscopy-negative reflux disease (NERD)*—PPIs and H₂-blocker's superior to placebo; PPIs not as good for nonerosive disease as they are for erosive disease because of heterogeneity of disease; *maintenance therapy*—Lundell showed that regardless of baseline grade of esophagitis, symptoms return if PPI stopped; 80% of patients on omeprazole remain symptom-free for one year; Klinkenberg-Knol showed that 80% of patients maintained healing and few relapses occurred with PPIs over 11-yr follow-up

Cost considerations: *out-of-pocket cost to uninsured individual for once-daily, 30 day supply*—omeprazole (Prilosec) \$119 to \$191; generic omeprazole 20 mg \$125, over-the-counter (OTC) omeprazole 20 mg \$15-\$21, esomeprazole (Nexium) \$135, lansoprazole (Prevacid) \$145 to \$150, rabeprazole (Aciphex) \$128, pantoprazole (Protonix) \$110

Step down-therapy: *Veterans Affairs studies*—in primary care setting, approximately 50% of patients could be weaned from PPIs over several years; during follow-up, 34% of patients managed with H₂-blocker alone, and 16% needed no medication; in another study of 117 GERD patients on bid dosing, 80% stepped down to once daily treatment; *implications*—in primary care setting, patients may not need PPIs lifelong or may be able to taper dose downward; primary care results may not be generalizable to specialty practices

Comparison with surgery: up to 90% symptomatic improvement with surgery; Lundell compared surgery to omeprazole titrated to symptoms in randomized controlled trial; found no difference in remission over 5 yr; data apply to surgeons experienced with reflux procedure; however, average surgeon in United States not necessarily expert; study data show that after surgery in community setting, one third of patients experience persistent heartburn, one third need antireflux medications, 7% need redo surgery, and two thirds have new symptoms; *Spechler's study*—looked at long-term follow-up in randomized trial of medical vs surgical therapy; 60% of surgical patients required antireflux medication postoperatively; *even with expert surgeons*—surgery does not work in approximately 1 of 10 patients; immediate postoperative complications in 5%; late complications include dysphagia,

diarrhea, and gas bloat; *mortality rate*—1 in 600 patients who have antireflux surgery

Comparison with endoscopic therapy: randomized controlled trial compared Stretta procedure vs sham Stretta for GERD; significant decrease in heartburn and improved quality-of-life measures in Stretta group (with all endoscopic approaches, physiology not clearly delineated); patients feel better, but median acid exposure, daily PPI use, median LES pressure, and erosions no different between groups; trial results not generalizable: patients in trials typically on daily PPIs, have modest increase in acid exposure, LES pressure not decreased, hiatal hernias typically small, and erosions rare; *study*—looked at Bernstein test before and after Stretta; before Stretta, 13 of 13 positive; after Stretta 9 of 13 positive; time to report of symptoms changed from 9 to 17 min on average; *implication*—something happening to nerves

Endoscopic therapy of GERD compared to existing therapy: few studies compare endoscopy to medication, and none compare endoscopy to antireflux surgery; paucity of controlled trials, limited follow-up, and confusing nature of data suggest reserving endoscopy for clinical trials, even though procedure FDA-approved; no randomized trials evaluate endoscopic suturing

Problems with PPIs: therapy probably lifelong; compliance potential problem; insurance may not pay for newer PPIs; potential long-term side effects include headaches, diarrhea, nausea, abdominal pain, back pain, and possible breast engorgement and enlargement in women; possible *Helicobacter pylori* interactions, eg, corpus gastritis and accelerated atrophy, and resultant enterochromaffin-like (ECL) cell hyperplasia; hypergastrinemia seen primarily in *H pylori*-positive individuals; one study on long-term effects of omeprazole found more gastric atrophy in *H pylori*-positive group than in *H pylori*-negative group; unknown if atrophy plays role in intestinal metaplasia-carcinoma sequence; Europeans test and treat for *H pylori* before prescribing long-term PPI; gastric hypoacidity, bacterial overgrowth, potential carcinogenic effects due to increased nitroso compounds, fundic gland polyps, vitamin B₁₂, all theoretical concerns

POSTOPERATIVE COMPLICATIONS OF SURGERY—Dr. Richter

Planning reflux surgery: inform patients of possible complications (eg, dysphagia, diarrhea, recurrent reflux, gas bloat, rectal gas and its social implications); most symptoms improve in 6 mo, although not always

Postoperative dysphagia: treatable; incidence increased with laparoscopic procedure; persistent rate 5% to 10% of patients; usually resolves in first 6 mo; if patient does not improve after bougie dilation, look for other underlying problem (eg, periesophageal hernia, slipped Nissen fundoplication, tight wrap, or esophageal stricture; majority require reoperation); nadir pressure (difference between gastric baseline and relaxation with swallow) predicts resolution of dysphagia; if nadir pressure >10 mm Hg, patients do well with pneumatic dilation (50% response in speaker's practice); surgeon must ensure that tight wrap only problem

Gas bloat: intragastric volume decreased after any antireflux surgery (partial or complete wrap) because function of fundus altered; over time (possibly due to wrap loosening), capacity improves and symptoms may abate; after antireflux surgery, encourage patients to eat only until fullness and avoid carbonated beverages; smokers should not smoke after eating; *rectal flatus*—associated with antireflux surgery because GERD patients tend to swallow large amounts of air but cannot belch

Postoperative diarrhea: 18% of patients in one study developed diarrhea after antireflux surgery; mild and self-limiting in most patients; 2 yr later, 13 of 15 patients still had diarrhea; 6 required medication; related to vagal injury in some cases; warn patients of possibility

Reasons for unsuccessful operations: unrecognized esophageal shortening; large nonreducible hiatal

hernias, long-segment Barrett's esophagus, or long, difficult-to-dilate esophageal strictures with true stenosis effectively shorten esophagus; prevalence in uncomplicated GERD approximately 2.5%, in Barrett's esophagus or esophageal strictures, 6% to 10%; *reoperations*—if esophagus under constant tension, fundoplication may appear to slip (actually, constant tension causes return of hernia and symptoms); patients typically present 6 mo to 2 yr postoperatively; among 112 redo operations, presenting symptoms included dysphagia, reflux, periesophageal hernia, and pain; increased morbidity and mortality with redo operations

Educational Objectives

The goal of this presentation is to inform the clinician about complications of gastroesophageal reflux disease (GERD) and its treatment. After hearing and assimilating this program, the clinician will be better able to:

1. Include GERD in the differential diagnosis of cough and difficult-to-manage asthma
2. Recognize laryngeal and pharyngeal symptoms indicative of atypical reflux disease.
3. Prescribe proton pump inhibitors appropriately.
4. Determine when reflux surgery is appropriate.
5. Identify complications of reflux surgery.

Discussed on This Program

Prednisone [multiple brand names]
 Theophylline [Theo-Dur, multiple brand names]
 Rabepazole sodium [Aciphex]
 Flunisolide [AeroBid, multiple brand names]
 Omeprazole [Prilosec, Prilosec OTC]
 Cisapride [Propulsid]
 Sucralfate [Carafate[®]]
 Lansoprazole [Prevacid]
 Pantoprazole sodium [Protonix, Protonix I.V.]
 Esomeprazole magnesium [Nexium]
 Ranitidine HCl [Zantac, Zantac 75, Zantac EFFERdose, Zantac GELDose]

Programs of Related Interest

Hunt RH, et al: reflux disease. *Audio-Digest Gastroenterology* 17:11(Nov 1), 2003; **Dumot JA, et al:** Esophageal procedures. *Audio-Digest Gastroenterology* 17:1(January 1), 2003

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Suggested Reading

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1999; **Harding SM, et al:** 24-h esophageal pH testing in asthmatics: respiratory symptom correlation with esophageal acid events. *Chest* 115:654-9, 1999; **Harding SM, et al:** Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med* 100:395-405, 1996; **Inadomi JM, et al:** Step-down management of gastroesophageal reflux disease. *Gastroenterology* 121:1095-100, 2001; **Inadomi JM, et al:** Step-down from multiple- to single-dose proton pump inhibitors (PPIs): a prospective study of patients with heartburn or acid regurgitation completely relieved with PPIs. *Am J Gastroenterol* 98:1940-4, 2003; **Irwin RS, et al:** Difficult-to-control asthma. Contributing factors and outcome of a systematic management protocol. *Chest* 103:1662-9, 1993; **Kahrilas PJ:** Laparoscopic antireflux surgery: silver bullet or the emperor's new clothes? *Am J Gastroenterol* 94:1721-3, 1999; **Klinkenberg-Knol EC, et al:** Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. *Gastroenterology* 118:661-9, 2000; **O'Connor JF, et al:** The cost-effectiveness of strategies to assess gastroesophageal reflux as an exacerbating factor in asthma. *Am J Gastroenterol* 94:1472-80, 1999; **Ours TM, et al:** A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol* 94:3131-8, 1999; **Richter JE, et al:** *Helicobacter pylori* and gastroesophageal reflux disease: the bug may not be all bad. *Am J Gastroenterol* 93:1800-2, 1998; **Richter JE:** Gastroesophageal reflux disease and asthma: the two are directly related. *Am J Med* 108 Suppl 4a:153S-158S, 2000; **Sontag SJ, et al:** Asthmatics with gastroesophageal reflux: long term results of a randomized trial of medical and surgical antireflux therapies. *Am J Gastroenterol* 98:987-99, 2003; **Sontag SJ:** Gastroesophageal reflux disease and asthma. *J Clin Gastroenterol* 30(3 Suppl):S9-30, 2000; **Spechler SJ:** Medical or invasive therapy for GERD: an acidulous analysis. *Clin Gastroenterol Hepatol* 1:81-8, 2003; **Vaezi MF:** Extraesophageal manifestations of gastroesophageal reflux disease. *Clin Cornerstone* 5:32-8, 2003; **Vakil N, et al:** Clinical effectiveness of laparoscopic fundoplication in a U.S. community. *Am J Med* 114:1-5, 2003.

Faculty Disclosure

In adherence to ACCME guidelines, the Audio-Digest Foundation requests all lecturers to disclose any significant financial relationship with the manufacturer or provider of any commercial product or service discussed. For this issue there is nothing to report.

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