GASTROESOPHAGEAL REFLUX DISEASE

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- Heartburn; may be exacerbated by meals, bending, or recumbency.
- Typical uncomplicated cases do not require diagnostic studies.
- Endoscopy demonstrates abnormalities in one third of patients.

..... General Considerations

GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms or complications. GERD affects 20% of adults, who report at least weekly episodes of heartburn, and up to 10% complain of daily symptoms. Although most patients have mild disease, esophageal mucosal damage (reflux esophagitis) develops in up to one-third and more serious complications develop in a few others. Several factors may contribute to GERD.

A. Dysfunction of the Gastroesophageal Junction

The antireflux barrier at the gastroesophageal junction depends on LES pressure, the intra-abdominal location of the sphincter (resulting in a "flap valve" caused by angulation of the esophageal-gastric junction), and the extrinsic compression of the sphincter by the crural diaphragm. In most patients with GERD, baseline LES pressures are normal (1 0-35 mm Hg) . Most reflux episodes occur during transient relaxations of the LES that are triggered by gastric distention by a vagovagal reflex. A subset of patients with GERD have an incompetent (less than 10 mm Hg) LES that results in increased acid reflux, especially when supine or when intra-abdominal pressures are increased by lifting or bending. A hypotensive sphincter is present in up to 50% of patients with severe erosive GERD. Hiatal hernias are found in one-fourth of patients with nonerosive GERD, three-fourths of patients with severe erosive esophagitis, and over 90% of patients with Barrett esophagus. They are caused by movement of the LES above the diaphragm, resulting in dysfunction of the gastroesophageal junction reflux barrier. Hiatal hernias are common and may cause no symptoms; however, in patients with gastroesophageal reflux, they are associated with higher amounts of acid reflux and delayed esophageal acid clearance, leading to more severe esophagitis and Barrett esophagus. Increased reflux episodes occur during normal swallowing-induced relaxation, transient LES relaxations, and straining due to reflux of acid from the hiatal hernia sac into the esophagus. Truncal obesity may contribute to GERD, presumably due to an increased intra-abdominal pressure, which

contributes to dysfunction of the gastroesophageal junction and increased likelihood of hiatal hernia.

B. Irritant Effects of Refluxate

Esophageal mucosal damage is related to the potency of the refluxate and the amount of time it is in contact with the mucosa. Acidic gastric fluid (pH less than 4.0) is extremely caustic to the esophageal mucosa and is the major injurious agent in the majority of cases. In some patients, reflux of bile or alkaline pancreatic secretions may be contributory. Most acid reflux episodes occur after meals, despite the buffering effect of food that raises intragastric pH. In fact, meal-stimulated acid secretion from the proximal stomach mixes poorly with gastric contents, forming an unbuffered "acid pocket" that floats on top of the meal contents. In patients with GERD, this acid pocket is located near the gastroesophageal junction and may extend into the LES or hiatal hernia.

C. Abnormal Esophageal Clearance

Acid refluxate normally is cleared and neutralized by esophageal peristalsis and salivary bicarbonate. One-half of patients with severe GERD have diminished clearance due to hypotensive peristaltic contractions (less than 30 mm Hg) or intermittent failed peristalsis after swallowing. Certain medical conditions such as scleroderma are associated with diminished peristalsis. Sjogren syndrome, anticholinergic medications, and oral radiation therapy may exacerbate GERD due to impaired salivation.

D. Delayed Gastric Emptying

Impaired gastric emptying due to gastroparesis or partial gastric outlet obstruction potentiates GERD.

Clinical Findings

A. Symptoms and Signs

The typical symptom is heartburn. This most often occurs 30-60 minutes after meals and upon reclining. Patients often report relief from taking antacids or baking soda. When this symptom is dominant, the diagnosis is established with a high degree of reliability. Many patients, however, have less specific dyspeptic symptoms with or without heartburn. Overall, a clinical diagnosis of gastroesophageal reflux has a sensitivity and specificity of only 65%. Severity is not correlated with the degree of tissue damage. In fact, some patients with severe esophagitis are only mildly symptomatic.

Patients may complain of regurgitation-the spontaneous reflux of sour or bitter gastric contents into the mouth. Dysphagia occurs in one-third of patients and may be due to

erosive esophagitis, abnormal esophageal peristalsis, or the development of an esophageal stricture.

"Atypical" or "extraesophageal" manifestations of gastroesophageal disease may occur, including asthma, chronic cough, chronic laryngitis, sore throat, noncardiac chest pain, and sleep disturbances. Gastroesophageal reflux, especially unrecognized nocturnal reflux, may be either a causative or an exacerbating factor in a subset of these patients. In the absence of heartburn or regurgitation, atypical symptoms are unlikely to be related to gastroesophageal reflux.

Physical examination and laboratory data are normal in uncomplicated disease.

B. Special Examinations

Initial diagnostic studies are not warranted for patients with typical GERD symptoms suggesting uncomplicated reflux disease. Patients with typical symptoms of heartburn and regurgitation should be treated empirically with a once daily proton pump inhibitor for 4-8 weeks. Symptomatic response to empiric treatment (while clinically desirable) only has a 78% sensitivity and 54% specificity for GERD. Therefore, further investigation is required in patients with symptoms that persist despite empiric proton pump inhibitor therapy to identify complications of reflux disease and to diagnose other conditions, particularly in patients with "alarm features" (troublesome dysphagia, odynophagia, weight loss, iron deficiency anemia).

1 . Upper endoscopy-Upper endoscopy is excellent for documenting the type and extent of tissue damage in gastroesophageal reflux; for detecting other gastroesophageal lesions that may mimic GERD; and for detecting GERD complications, including esophageal stricture, Barrett metaplasia, and esophageal adenocarcinoma. In the absence of prior antisecretory therapy, up to one-third of patients with GERD have visible mucosal damage (known as reflux esophagitis), characterized by single or multiple erosions or ulcers in the distal esophagus at the squamocolumnar junction. In patients treated with a proton pump inhibitor prior to endoscopy, preexisting reflux esophagitis may be partially or completely healed. The Los Angeles (LA) classification grades reflux esophagitis on a scale of A (one or more isolated mucosal breaks 5 mm or less that do not extend between the tops of two mucosal folds) to D (one or more mucosal breaks that involve at least 75% of the esophageal circumference) .

2. Barium esophagography-This study should not be performed t o diagnose GERD. I n patients with severe dysphagia, it is sometimes obtained prior to endoscopy to identify a stricture.

3. Esophageal pH or combined esophageal pH-impedance testing-Esophageal pH monitoring is unnecessary in most patients but may be indicated to document abnormal esophageal acid exposure in patients who have atypical or extraesophageal symptoms or who are being considered for antireflux surgery. Combined impedance-pH monitoring is indicated in patients with persistent symptoms despite proton pump inhibitor therapy to determine whether symptoms are caused by acid or nonacid reflux (40%) or are unrelated to reflux and indicative of a functionaldisorder.

Differential Diagnosis

Symptoms of GERD may be similar to those of other diseases such as esophageal motility disorders, peptic ulcer, angina pectoris, or functional disorders. Reflux erosive esophagitis may be confused with pill-induced damage, eosinophilic esophagitis, or infections (CMV, herpes, Candida).

Complications

A. Barrett Esophagus

This is a condition in which the squamous epithelium of the esophagus is replaced by metaplastic columnar epithelium containing goblet and columnar cells (specialized intestinal metaplasia) . Present in up to 10% of patients with chronic reflux, Barrett esophagus is believed to arise from chronic reflux-induced injury to the esophageal squamous epithelium; however, it is also increased in patients with truncal obesity independent of GERD. Barrett esophagus is suspected at endoscopy from the presence of orange, gastric type epithelium that extends upward from the stomach into the distal tubular esophagus in a tongue-like or circumferential fashion. Biopsies obtained at endoscopy confirm the diagnosis. Three types of columnar epithelium may be identified: gastric cardiac, gastric fundic, and specialized intestinal metaplasia. There is agreement that the latter carries an increased risk of dysplasia; however, some authorities believe that gastric cardiac mucosa also raises risk. Barrett esophagus does not provoke specific symptoms but gastroesophageal reflux does. Most patients have a long history of reflux symptoms, such as heartburn and regurgitation.

Barrett esophagus should be treated with long-term proton pump inhibitors once or twice daily to control reflux symptoms. Although these medications do not appear to cause regression of Barrett esophagus, they may reduce the risk of cancer. Paradoxically, one-third of patients report minimal or no symptoms of GERD, suggesting decreased acid sensitivity of Barrett epithelium. Indeed, over 90% of individuals with Barrett esophagus in the general population do not seek medical attention. The most serious complication of Barrett esophagus is esophageal

adenocarcinoma. It is believed that most adenocarcinomas of the esophagus and many such tumors of the gastric cardia arise from dysplastic epithelium in Barrett esophagus. In recent studies, the incidence of adenocarcinoma in patients with Barrett esophagus has been estimated at 0 . 1 2-0.33%/year. Although this still is an 11 -fold increased risk compared with patients without Barrett esophagus, adenocarcinoma of the esophagus remains a relatively uncommon malignancy in the United States (7000 cases/year). Given the large number of adults with chronic GERD relative to the small number in whom adenocarcinoma develops, 2011 clinical guidelines recommend against endoscopic screening for Barrett esophagus in adults with GERD except in those with multiple risk factors for adenocarcinoma (chronic GERD, hiatal hernia, obesity, white race, male gender, and age 50 years of older). In patients known to have Barrett esophagus, surveillance endoscopy every 3-5 years is recommended to look for low- or high-grade dysplasia or adenocarcinoma. The risk of progression to adenocarcinoma is a 0.8% risk per year for patients with low-grade dysplasia and a 6% risk per year for high-grade dysplasia. Patients with low-grade dysplasia require repeat endoscopic surveillance in 6 months to exclude coexisting high-grade dysplasia or cancer and, if low-grade dysplasia persists, endoscopic surveillance should be repeated yearly. Approximately 1 3 % of patient with high-grade dysplasia may harbor an unrecognized invasive esophageal cancer. Therefore, patients with high-grade dysplasia should undergo repeat staging endoscopy with resection of visible mucosal nodules and random mucosal biopsies in order to exclude invasive cancer. The subsequent management of patients with intramucosal cancer or high-grade dysplasia has rapidly evolved. Until recently, esophagectomy was recommended for patients deemed to have a low operative risk; however, this procedure is associated with high morbidity and mortality rates (40% and 1 -5%, respectively) . Therefore, it is now recommended that endoscopic therapy be performed for most patients with high-grade dysplasia or intramucosal adenocarcinoma. Endoscopic therapiescan remove or ablate dysplastic Barrett epithelium, using mucosal snare resection and radiofrequency wave ablation electrocautery. Snare resection is performed of visible neoplastic mucosal nodules to exclude submucosal invasion (which favors surgical resection) . Of the patients who have cancer confined to the mucosa, less than 2% have recurrence of cancer or high-grade dysplasia after snare resection. Radiofrequency wave ablation electrocautery is used to ablate Barrett epithelium with flat (non-nodular) dysplasia and to ablate Barrett epithelium that remains after snare resection of dysplastic mucosal nodules. The efficacy of endoscopic ablation therapies in patients with Barrett dysplasia is supported by several studies. When high-dose proton pump inhibitors are administered to normalize intraesophageal pH, radiofrequency wave ablation

electrocautery eradication of Barrett columnar epithelium is followed by complete healing with normal squamous epithelium in greater than 90% of patients. In a 20 1 1 randomized, sham-controlled trial in 127 patients with Barrett dysplasia with 3 -year follow up, eradication of high-grade dysplasia occurred in 98% after radiofrequency ablation (HALO) and progression to cancer was only 0.55%/year. After initial ablation, Barrett esophagus recurs (with or without dysplasia) in up to 33% within 2 years, justifying periodic surveillance endoscopy. Endoscopic ablation techniques have a risk of complications (bleeding, perforation, strictures) . Therefore, endoscopic eradication therapy currently is not recommended for patients with nondysplastic Barrett esophagus for whom the risk of developing esophageal cancer is low and treatment does not appear to be cost -effective.

B. Peptic Stricture

Stricture formation occurs in about 5% of patients with esophagitis. It is manifested by the gradual development of solid food dysphagia progressive over months to years. Often there is a reduction in heartburn because the stricture acts as a barrier to reflux. Most strictures are located at the gastroesophageal junction. Endoscopy with biopsy is mandatory in all cases to differentiate peptic stricture from stricture by esophageal carcinoma. Active erosive esophagitis is often present. Up to 90% of symptomatic patients are effectively treated with dilation with graduated polyvinyl catheters passed over a wire placed at the time of endoscopy or fluoroscopically, or balloons passed fluoroscopically or through an endoscope. Dilation is continued over one to several sessions. A luminal diameter of 1 3 - 1 7 mm is usually sufficient to relieve dysphagia. Long-term therapy with a proton pump inhibitor is required to decrease the likelihood of stricture recurrence. Some patients require intermittent dilation to maintain luminal patency, but operative management for strictures that do not respond to dilation is seldom required. Refractory strictures may benefit from endoscopic injection of triamcinolone into the stricture.

Treatment

A. Medical Treatment

The goal of treatment is to provide symptomatic relief, to heal esophagitis (if present), and to prevent complications. In the majority of patients with uncomplicated disease, empiric treatment is initiated based on a compatible history without the need for further confirmatory studies. Patients not responding and those with suspected complications undergo further evaluation with upper endoscopy or esophageal manometry and pH recording.

1 . **Mild, intermittent symptoms**-Patients with mild or intermittent symptoms that do not impact adversely on quality of life may benefit from lifestyle modifications with medical interventions taken as needed. Patients may find that eating smaller meals and elimination of acidic foods (citrus, tomatoes, coffee, spicy foods), foods that precipitate reflux (fatty foods, chocolate, peppermint, alcohol) , and cigarettes may reduce symptoms. Weight loss should be recommended for patients who are overweight or have had recent weight gain. All patients should be advised to avoid lying down within 3 hours after meals (the period of greatest reflux) . Patients with nocturnal symptoms should also elevate the head of the bed on 6-inch blocks or a foam wedge to reduce reflux and enhance esophageal clearance. Patients with infrequent heartburn (less than once weekly) may be treated on demand with antacids or oral H2-receptor antagonists. Antacids provide rapid relief of heartburn; however, their duration of action is less than 2 hours. Many are available over the counter. Those containing magnesium should not be used for patients with kidney disease, and patients with acute or chronic kidney disease should be cautioned appropriately. All oral H2-receptor antagonists are available in over-the-counter formulations: cimetidine 200 mg, ranitidine and nizatidine 75 mg, famotidine 10 mg-all of which are half of the typical prescription strength. When taken for active heartburn, these agents have a delay in onset of at least 30 minutes. However, once these agents take effect, they provide heartburn relief for up to 8 hours. When taken before meals known to provoke heartburn, these agents reduce the symptom.

2. Troublesome symptoms

A. INITIAL THERAPY-Patients with troublesome reflux symptoms and patients with known complications of GERD should be treated with a once-daily oral proton pump inhibitor (omeprazole or rabeprazole, 20 mg; omeprazole, 40 mg with sodium bicarbonate; lansoprazole, 30 mg; dexlansoprazole, 60 mg; esomeprazole or pantoprazole, 40 mg) taken 30 minutes before breakfast for 4-8 weeks. Because there appears to be little difference between these agents in efficacy or side effect profiles, the choice of agent is determined by cost. Oral omeprazole, 20 mg, and lansoprazole, 15 mg, are available as over-thecounter formulations. Once-daily proton pump inhibitors achieve adequate control of heartburn in 80-90% of patients, complete heartburn resolution in over 50%, and healing of erosive esophagitis (when present) in over 80%. Because of their superior efficacy and ease of use, proton pump inhibitors are preferred to H2-receptor antagonists for the treatment of acute and chronic GERD. Approximately 10-20% of patients do not achieve symptom relief with a once-daily dose within 2-4 weeks and require a twice-daily proton pump inhibitor (taken 30

minutes before breakfast and dinner) . Patients with inadequate symptom relief with empiric twice-daily proton pump inhibitor therapy should undergo evaluation with upper endoscopy. Many providers prefer to prescribe initial twice-daily proton pump inhibitor therapy for patients who have documented severe erosive esophagitis (Los Angeles Grade C or D), Barrett esophagus, or peptic stricture.

B. LONG-TERM THERAPY-In those who achieve good symptomatic relief with a course of empiric once-daily proton pump inhibitor, therapy may be discontinued after 8-12 weeks. Most patients (over 80%) will experience relapse of GERD symptoms, usually within 3 months. Patients whose symptoms relapse may be treated with either continuous proton pump inhibitor therapy, intermittent 2-4 week courses, or "on demand" therapy (ie, drug taken until symptoms abate) depending on symptom frequency and patient preference. Alternatively, twice daily H2-receptor antagonists may be used to control symptoms in patients without erosive esophagitis. Patients who require twice-daily proton pump inhibitor therapy for initial symptom control and patients with complications of GERD, including severe erosive esophagitis, Barrett esophagus, or peptic stricture, should be maintained on longterm therapy with a once- or twice-daily proton pump inhibitor titrated to the lowest effective dose to achieve satisfactory symptom control. Side effects of proton pump inhibitors are uncommon. Headache, diarrhea, and abdominal pain may occur with any of the agents but generally resolve when another formulation is tried. Potential risks of long-term use of proton pump inhibitors include an increased risk of infectious gastroenteritis (including C difficile), iron and vitamin B 12 deficiency, hypomagnesemia, pneumonia, hip fractures (possibly due to impaired calcium absorption) , and fundic gland polyps (which appear to be of no clinical significance) .

3. **Extraesophageal reflux manifestations**-Establishing a causal relationship between gastroesophageal reflux and extraesophageal symptoms (eg, asthma, hoarseness, cough, sleep disturbances) is difficult. Gastroesophageal reflux seldom is the sole cause of extraesophageal disorders but may be a contributory factor. Although ambulatory esophageal pH testing can document the presence of increased acid esophageal reflux, it does not prove a causative connection. Current guidelines recommend that a trial of a twice-daily proton pump inhibitor be administered for 2-3 months in patients with suspected extraesophageal GERD syndromes who also have typical GERD symptoms. Improvement of extraesophageal symptoms suggests but does not prove that acid reflux is the causative factor. Esophageal impedance-pH testing may be performed in patients whose extraesophageal symptoms persist after

3 months of twice-daily proton pump inhibitor therapy and may be considered before proton pump inhibitor therapy in patients without typical GERD symptoms in whom other causes of extraesophageal symptoms have been excluded.

4. **Unresponsive disease**-Approximately 5% do not respond to twice-daily proton pump inhibitors or a change to a different proton pump inhibitor. These patients should undergo endoscopy for detection of severe, inadequately treated reflux esophagitis and for other gastroesophageal lesions (including eosinophilic esophagitis) that may mimic GERD. The presence of active erosive esophagitis usually is indicative of inadequate acid suppression and can almost always be treated successfully with higher proton pump inhibitor doses (eg, esomeprazole, 40 mg twice daily) . Alginate is a naturally occurring polymer that forms a viscous raft that floats on the gastric acid pocket and significantly reduces postprandial reflux episodes in patients with GERD and large hiatal hernias. A proprietary antacid-alginate formulation (Gaviscon Double Action Liquid) is available in Europe but not the United States. Truly refractory esophagitis may be caused by gastrinoma with gastric acid hypersecretion (Zollinger-Ellison syndrome), pill-induced esophagitis, resistance to proton pump inhibitors, and medical noncompliance. Patients without endoscopically visible esophagitis should undergo ambulatory impedance-pH monitoring while taking a twice-daily proton pump inhibitor to determine whether the symptoms are correlated with acid or nonacid reflux episodes. The pH study is performed on therapy if the suspicion for GERD is high (to determine whether therapy has adequately suppressed acid esophageal reflux) and off therapy if the suspicion for GERD is low (to determine whether the patient has reflux disease). Combined esophageal pH monitoring with impedance monitoring is preferred over pH testing alone because of its ability to detect both acid and nonacid reflux events. Approximately 60% of patients with unresponsive symptoms do not have increased reflux and may be presumed to have a functional disorder. Treatment with a low-dose tricyclic antidepressant (eg, imipramine or nortriptyline 25 mg at bedtime) may be beneficial.

B. Surgical Treatment

Surgical fundoplication affords good to excellent relief of symptoms and healing of esophagitis in over 85% of properly selected patients and can be performed laparoscopically with low complication rates in most instances. Although patient satisfaction is high, typical reflux symptoms recur in 1 0-30% of patients. Furthermore, new symptoms of dysphagia, bloating, increased flatulence, dyspepsia, or diarrhea develop in over 30% of patients. In 20 1 1 , results from a randomized trial comparing laparoscopic fundoplication with prolonged medical therapy (esomeprazole 40 mg/day) for chronic GERD were reported. After 5 years, adequate GERD symptom control

(symptom remission) was similar, occurring in 85-92% of patients; however, patients who had undergone fundoplication had increased dysphagia, bloating, and flatulence. In 2012, the FDA approved a novel, minimally invasive magnetic artificial sphincter for the treatment of GERD. The device is made up of a flexible, elastic string of titanium beads (wrapped around a magnetic core) that is placed laparoscopically below the diaphragm at the gastroesophageal junction. A 2013 prospective study of 100 patients reported that 64% of patients had significant reductions in esophageal acid reflux. Further experience with this device is needed before widespread adoption can be recommended. Surgical treatment is not recommended for patients who are well controlled with medical therapies but should be considered for : (1) otherwise healthy, carefully selected patients with extraesophageal manifestations of reflux, as these symptoms often require high doses of proton pump inhibitors and may be more effectively controlled with antireflux surgery; (2) those with severe reflux disease who are unwilling to accept lifelong medical therapy due to its expense, inconvenience, or theoretical risks; and (3) patients with large hiatal hernias and persistent regurgitation despite proton pump inhibitor therapy. Gastric bypass (rather than fundoplication) should be considered for obese patients with GERD.

When to Refer

- Patients with typical GERD whose symptoms do not resolve with empiric management with a twice-daily proton pump inhibitor.
- Patients with suspected extraesophageal GERD symptoms that do not resolve with 3 months of twice-daily proton pump inhibitor therapy.
- Patients with significant dysphagia or other alarm symptoms for upper endoscopy.
- Patients with Barrett esophagus for endoscopic surveillance.
- Patients who have Barrett esophagus with dysplasia or early mucosal cancer.