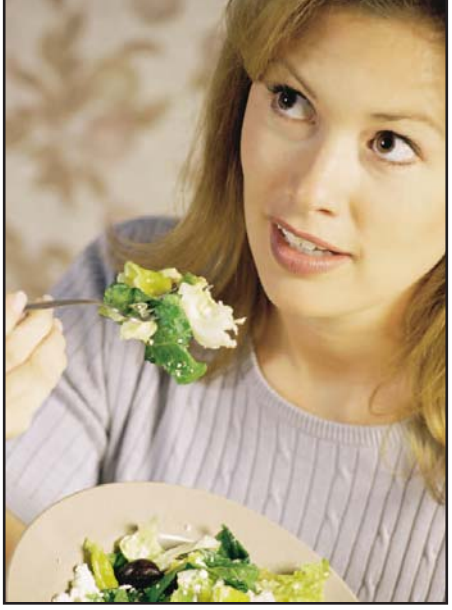
Heart-Burning Issues

Helping Patients With Gastroesophageal Reflux Disease



By Khursheed N. Jeejeebhoy, MB, BS, PhD, FRCP, FRCPC

Case 1

A 40-year-old male presents with a two year history of a burning sensation in the substernal region after heavy meals, followed by acid eructation of sour fluid. Between meals he is asymptomatic. He has been gaining weight, smokes 20 cigarettes each day and drinks five to eight cups of coffee.

He has not had dysphagia or odynophagia. His family doctor recorded that he was an obese male and his hemoglobin was 145 g/L. *Helicobacter Pylori* (*H. Pylori*) serology was positive and a upper gastrointestinal (GI) series showed a hiatus hernia. His family physician treated the *H. Pylori* and during treatment the patient was asymptomatic, but symptoms returned after medications were discontinued. He was placed on an alginate antacid and an H_2-receptor antagonist (H_2RA) and responded quite well for a few months but then the symptoms returned, occurring daily and creating the need to take increasing doses of antacid and H_2RA.

Despite treatment, symptom relief was incomplete. He was then changed to a proton pump inhibitor (PPI) with complete relief. After three months on PPI therapy, smoking cessation and a 30 pound weight loss, he was able to control the remaining symptoms of occasional heartburn with antacids alone.

Case 2

A 50-year-old white male presents with dysphagia to solids. He finds it increasingly difficult to swallow pieces of meat and bread. He can identify the place where the food bolus appears to stick. On a few occasions he has had to regurgitate the food to get relief.

He has a long history of heartburn, which he relieves by keeping a bottle of antacids handy. Occasionally, he has pain in the substernal region that radiates to the middle of his back and left shoulder. He has heartburn most of the day, aggravated by lifting, bending and lying in bed. He has also noted an increased hoarseness in his voice and attacks of wheezing. Recently, because of his inability to eat meat and bread he has lost 10 pounds. He has also developed mild iron deficiency anemia. He was referred to a gastroenterologist for endoscopy.

In this article

1. What is gastroesophageal reflux disease and what are the symptoms?
2. How do we manage the two patient case scenarios?
3. What alters the lower esophageal sphincter pressure?
4. Does eradicating *H. pylori* increase reflux?
5. What are some of the atypical presentations?

Heartburn is very common. In a survey, it occured in 44% of people on monthly intervals, in 14% of people weekly and in 7% of people daily. The cause of heartburn is reflux of acid into the esophagus. Acid reflux is a normal phenomenon but in most people it is asymptomatic. Only 5% to 7% of demonstrable acid reflux, based on esophageal pH measurements, are symptomatic. The duration of reflux, the ability of the esophagus to clear refluxed acid and the sensitivity of the esophagus to acid all determine whether the reflux will cause symptoms such as heartburn.

In some individuals, a motility disturbance of the esophagus is experienced as heartburn without reflux. The reflux of acid does not always damage the esophagus and gastroesophageal reflux disease (GERD) may be non-ulcerative (NU).This can cause esophageal ulceration (EU) or result in Barrett's esophagus (BE), when the esophagus becomes lined with metaplastic intestinal epithelium. The metaplastic epithelium of BE can become dysplastic and lead to adenocarcinoma of the esophagus. NU, EU and BE esophagus may represent increasing degrees of esophageal injury based on the fact that pH monitoring of the esophagus shows that 90% of patients with BE, 75% with EU and only 50% with NU have prolonged or frequent reflux.[1] Patients, however, tend to remain in the category in which they were first diagnosed (NU, EU or BE) and do not progress or regress between categories.[2]

What are the factors altering LES pressure?

Smoking is the single most important habit which increases reflux by reducing lower esophageal sphincter (LES) pressure. Coffee, even decaffeinated, also reduces LES pressure, as does chocolate and mint. High fat diets are also a factor in reducing LES pressure. The reduced LES pressure may or may not cause clinical symptoms depending on other factors as discussed above.

Dr. Jeejeebhoy is professor, faculty of medicine, University of Toronto and staff, St. Michael's Hospital, Toronto, Ontario.

Does eradicating *H. pylori* increase reflux?

Helicobacter Pylori (H. Pylori) causes gastritis, which reduces acid secretion and there are reports that eradicating *H. Pylori* increases

symptoms of reflux. On the other hand, the prolonged use of proton pump inhibitors (PPIs) in patients with *H. Pylori* associated with reflux, causes gastric atrophy. Since atrophic gastritis is a predisposing factor for gastric cancer, the development of gastric atrophy is considered to be undesirable.

How do I Manage Case 1?

The case pertains to a young person with uncomplicated reflux as exemplified by a lack of weight loss, dysphagia, odynophagia or anemia. Routine endoscopy is not necessary for this patient. He became asymptomatic when he started his treatment with proton pump inhibitors (PPIs). He relapsed when medication was stopped, presumably because the PPI was discontinued, therefore, he may need long-term PPI treatment. Was treatment of *H. Pylori* necessary? This is a very controversial topic. However, it is justified if the patient needs long-term PPIs because of the risk of gastric atrophy. In addition, treatment of *H. Pylori* has many other considerations than the ones related to reflux. If detected, most physicians would treat this condition, at least to eradicate the potential risk of gastric cancer.

What about conventional therapy?

Since, on initial presentation, patient 1 had heartburn only after heavy meals, a very conservative course of treatment may be used. The conventional treatment is to follow a step-up course starting with advice to stop smoking, reduce weight, raise the head of the bed by 10 inches, and to avoid coffee, chocolate and mint. alginate antacids and H_2-receptor antagonists (H_2RA) are prescribed. In controlled trials, Alginate provided better relief from heartburn than placebo, and the addition of an H_2RA prolongs the relief.[3,4] If the use of alginate antacid and H_2RA fails to provide complete relief, then PPI should be used.

What is the role of empirical PPI treatment?

In contrast to the conventional advice given above, a recent Canadian conference on reflux concluded that the best treatment for patient 1 is the step-down approach.[5] The patient is given full doses of a PPI for two to four weeks and then reassessed. If the symptoms improve, intermittent PPI or H_2RA are given. In young patients with a short history and no "red flags," such as dysphagia, involuntary weight loss and anemia, PPI treatment is given empirically using the step-down approach. However, if the need to give PPI becomes prolonged, then the patient should be referred for

How do I Manage Case 2?

This patient has a long history of persistent reflux suggestive of reduced esophageal tone. He has several "red flags," such as dysphagia, older age, anemia and weight loss. The dysphagia in this patient is dependent upon the nature and size of bolus. In addition, he needs to bring it up to get relief, all features of mechanical obstruction of the esophagus. Mechanical dysphagia in this patient suggests disruption of the esophageal lining with edema or stricture. Weight loss and anemia raises the possibility of complicating neoplasia or ulceration with a stricture restricting dietary intake and causing anemia from occult blood loss. In addition, he has atypical features, such as chest pain, hoarseness in his voice and wheezing. This patient clearly needs endoscopic evaluation and biopsy of any ulcerated lesions. Empirical treatment of this patient with PPIs or H_2 blockers is not justified and should be deferred until endoscopy has determined the cause of symptoms. Premature use of PPIs in this type of patient prior to endoscopy may mask the exact degree of ulceration and could even heal over a small cancer.

In this patient, the findings on endoscopy may be ulceration or the presence of Barrett's esophagus (BE). The latter usually occurs in white males and this patient is a person in whom BE may occur.

endoscopy. The unresolved question is: when does the use of a PPI become prolonged? It has been shown that after treating reflux successfully with a PPI for two to four months, about 50% of patients relapsed within six months and continued to require maintenance treatment while they were followed up for three years. Therefore, it is likely that the need for maintenance therapy beyond six months would predict that prolonged treatment would be required.

What are some of the atypical presentations of reflux?

While heartburn, regurgitation of acidic material, and dysphagia are the usual symptoms of reflux, this condition may present in other ways which may not be recognized immediately. Pain in the chest that radiates to the upper back can be a symptom of acid reflux. In others, the pain may simulate cardiac pain and radiate into the neck and down the left arm. In the elderly, chronic nausea, vomiting and anorexia can cause alarming weight loss. Chronic cough, bronchospasm and asthmatic symptoms may be presenting symptoms. In others, asthma may be aggravated. Chronic hoarseness of voice may be present. Reflux-like symptoms often occur in patients with irritable bowel syndrome (IBS) and is associated with bloating, excessive burping and epigastric pain.

In addition, patients with atypical symptoms or GERD partially responsive or unresponsive to PPI should have a 24-hour pH study. This study consists of inserting a pH probe into the esophagus connected to a portable computer that records (hand-held size). The esophageal pH is monitored over 24 hours during which the patient carries out normal activities. The patient marks the waking and sleeping periods as well as any symptoms. This study demonstrates which symptoms are related to episodes of acid reflux (esophageal pH less than 4.0) and factors which induce reflux.

In patients with atypical symptoms, motility studies may be used to demonstrate the presence of esophageal spasm, achalasia and to study the LES tone (Table 1).

How do I manage ulcerative esophagitis?

PPIs are the only medications which have been shown to result in the healing of esophageal ulcers. The degree of response depends upon achieving a pH greater than four for at least 12 hours.[6] PPIs are inactivated by the cytochrome p-450 family, type 2C19, of which there is a less active mutant form. This is more prevalent in Asian patients.[7] Therefore, the ability of a given dose of PPI to suppress acid for 12 hours depends upon the genetic makeup of the patient. A single dose was shown to maintain a pH greater than four for 12 hours in only 55% of patients, while in 21% of patients the response was only zero hours to six hours.[8] Recognising that patients may not respond to a fixed dose of a PPI, the dose may have to be escalated. The patient should be started at full

Table 1

Role of specialised investigations

Recommendations for the use of specialized investigations have been made by a Canadian Consensus Conference.[6] They are the presence of:

1. Dysphagia
2. Odynophagia
3. Bleeding
4. Weight loss
5. Chest Pain
6. Lack of response to four to eight weeks of PPI therapy
7. Once in a lifetime for patients on chronic therapy to determine the presence of Barrett's esophagus (BE)

While the American society for gastrointestinal endoscopy and the American college of gastroenterology also support the indications given above, they have added other indications, which are:

1. Esophageal symptoms in immunosuppressed patients
2. Those with changes on a barium study
3. Choking
4. Screening for BE
5. Prior to surgical repair of a hiatus hernia

Adapted from: Beck IT, Champion MC, Lemaire S, et al. The second canadian consensus conference on the management of patients with gastroesophgeal reflux disease. Can J Gastroenterol 1997; 11(suppl B): 7B-20B.

dose once a day for 12 weeks. If full dose does not relieve symptoms it should be increased to a full dose twice a day and finally, if necessary, to double dose twice a day. This patient will likely require continuous long-term PPI therapy. In patients on PPIs with EU, healing is often incomplete despite a lack of symptoms. It is useful to repeat endoscopy to determine if healing has occurred and to adjust the dose accordingly.

How do I manage Barrett's Esophageus?

PPI dosage in this case is the same as for ulcerative esophagitis. BE does not heal with the use of PPIs and the patient will require repeated endoscopy and multiple biopsies to detect the development of dysplasia. The frequency of endoscopic surveillance is controversial. Yearly endoscopy has been recommended even in patients without dysplasia based on the estimate that the development of cancer is about 1% per year. A recent consensus document of the American Gastroenterological Association (AGA) recommends surveillance every three to five years if there is no dysplasia, based on a estimate that the real incidence of cancer in patients with BE is about 0.4%. Patients with low-grade dysplasia need surveillance every six to 12 months. If there is high-grade dysplasia, an esophagectomy is the therapy of choice.

What is the role of anti-reflux surgery?

In many patients, the need for PPI therapy is continuous and of indefinite duration. The question arises as to the risks of prolonged PPI therapy and the possible benefits of anti-reflux surgery, such as freedom from drug therapy and reduced risk of developing adenocarcinoma.

Anti-reflux surgery involves wrapping the gastric fundus around the esophagus and results in an increase in LES pressure, healing of UE and the reversal of a stricture.

The question as to whether anti-reflux surgery prevents the development of adenocarcinoma has not yet been resolved by any good controlled trials. In a large retrospective cohort study of patients who had undergone surgery (66,965 patients) the incidence of adenocarcinoma was 14 times that of the general population.[9] This compares unfavourably, with a relative risk of six times that of the general population for those who don't have the surgery. This publication, therefore, does not support a protective role for anti-reflux surgery.

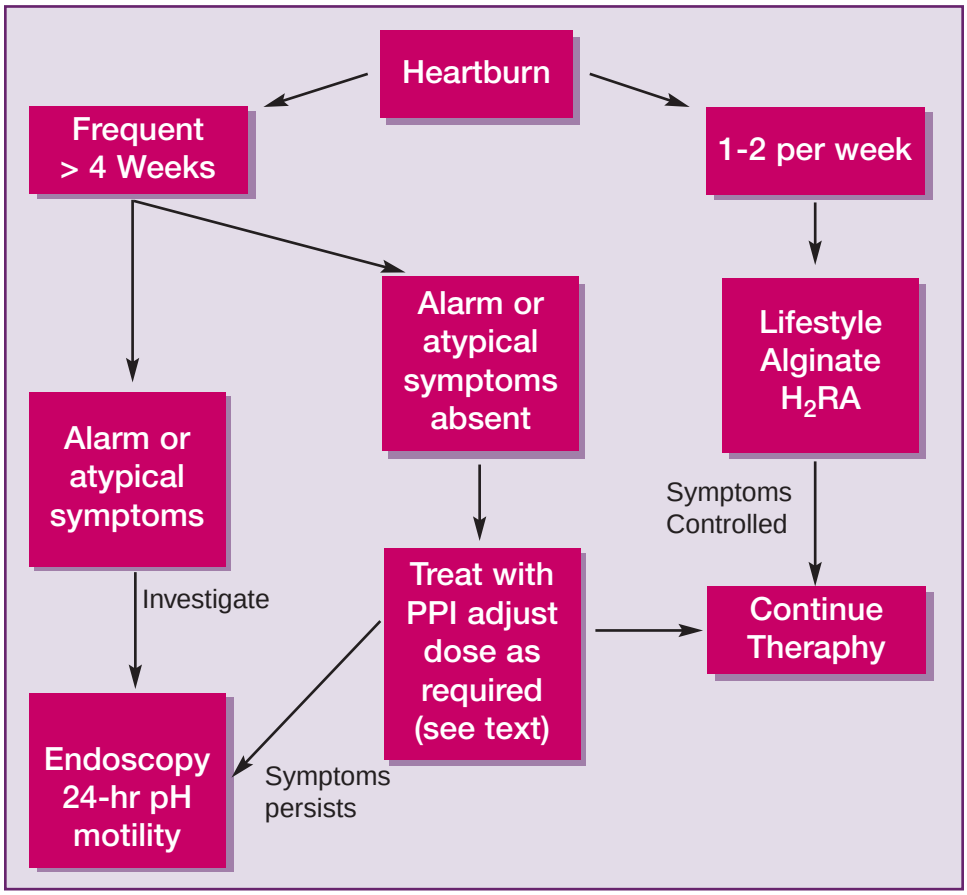


Figure 1. Gastroesophageal Reflux Cycle of Treatment

Anti-reflux surgery *versus* long-term PPI

In a randomised controlled trial, anti-reflux surgery and long-term PPI were equivalent if the dose of PPI was adjusted to provide relief of symptoms.[10] However, if a fixed dose of PPI was used, then surgery gave more relief.

After anti-reflux surgery, between 11% to 13% of patients required PPI or H_2RA and over a five-year followup, as many as 65% were using medical therapy for control of symptoms.[11] In addition, 30% had bloating, dysphagia and increased flatulence which impaired their quality of life.[12]

It is clear that surgery does not provide special benefits over the use of PPI because patients may have debilitating gas-bloat. This condition especially occurs in patients with a prior history of IBS. Patients with IBS who are sent for anti-reflux surgery should be warned about this complication as should all others. As well they should be told that they may require medical treatment in the future.

Does long-term PPI result in significant complications? Omeprazole, the first PPI to be introduced was shown to produce hyperplasia and neoplasia of enterochromaffin-like cells (ECL) in rodents due to prolonged acid suppression. However, in humans there are very few, if any side effects, over a five-year period of continuous therapy.[13] Over the five years there was no dysplasia or neoplastic changes. Other considerations of long-term therapy include risk of vitamin B_{12} deficiency, increased acid output after stopping therapy, atrophic gastritis in patients infected with *H. Pylori*, and acid suppression leading to enteric infections. None of these have been shown to be of clinical significance except for gastric atrophy in patients who are infected with *H. Pylori*. Eradication of *H. Pylori* would solve this problem.

Summary

Gastroesophageal reflux disease has a spectrum of presentations. Occasional reflux in young patients requires lifestyle modifications and over-the-counter medications such as alginate or low dose H_2RA (Figure 1). Young patients with a short history and no alarm symptoms should receive empirical PPI treatment followed by treatment on demand. If symptoms are prolonged and there are "red flags," then investigate (Figure 1). The role of surveillance endoscopy for BE and surgical therapy are controversial but surgery is not to be recommended without a clear understanding about side effects and the subsequent need for medical therapy. Dx

References

1. Martinez SD, Malagon IB, Garewal H, et al.: Non-erosive reflux disease (NERD)—Is it really just a mild form of gastroesophageal reflux disease (GERD)? Gastroenterology 2001; 120(suppl 1): 2163 (abstract).
2. Isolauri J, Luostarinen M, Isolauri E, et al.: Natural course of gastroesophageal reflux disease: 17–22 year follow-up of 60 patients. Am J Gastroenterol 1997; 92: 37–41.
3. Lanza FL, Smith V, Page-Castell JA, et al: Effectiveness of foaming antacid in relieving induced heartburn. South Med J. 1986; 79: 327-330.
4. Pappa KA, Williams BO, Payne JE, et al: A double-blind, placebo-controlled study of efficacy and safety of non-prescription ranitidiane 75 mg in prevention of meal-induced heartburn. Aliment. Pharmacol. Ther.1999; 13: 467-473.
5. Thomson ABR, Chiba N, Armstrong D, et al: Second canadian gastroesophageal disease consensus :Moving forward to new concepts. Can J Gastroenterol 1998; 12:551-6.
6. Bell Nj, Hunt RH: Role of gastric acid suppression in the treatment of gastro-oesophageal reflux disease. Gut 1992; 33:118-24.
7. Murray JA: Reflux esophagitis: Healed! Now what? Am J Gastroenterol 2000; 95:337-8.
8. Dent J: Roles of gastric acid and pH in the pathogenesis of gastroesophageal reflux disease. Scan J Gastroenterol 1994; 29(suppl201):55.
9. Ye W, Chow WH, Lagergren J, et al: Risk of adenocarcinoma of the esophagus and gastric cardia in patients with esophageal reflux disease and after reflux surgery. Gastroenterology 2001; 121:1286-93.
10. Lundell L, Miettinen P, Myrvold HE, et al. Continued (5-year) followup of a randomized clinical study comparing antireflux surgery and omeprazole in gastroesophageal reflux disease. J Am Coll Surg 2001; 192:172-9.
11. Spechler SJ, Lee E, Ahnen D, et al: Long term outcome of medical and surgical therapies for gastroesophageal reflux disease: followup of a randomized controlled trial. JAMA 2001; 285:2331-8.
12. El-Serang HB, Sonnenberg A: Outcome of erosive esophagitis after Nissan fundoplication. Am J Gastroenterol 1999; 94:1771-6.
13. Klinkenberg-Knol EC, Festen HP, Jansen JB, et al: Long-term treatment with omeprazole for refratory reflux esophagitis:efficacy and safety. Ann Intern Med 1994;121:161-7.