How to manage refractory GERD

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SUMMARY

Patients who are unresponsive to 4–8 weeks' treatment with PPIs twice daily might have so-called refractory GERD. The first investigation these patients should undergo is upper endoscopy to exclude a diagnosis of peptic ulcer disease or cancer and identify the presence of esophagitis. The presence of esophagitis in these patients is suggestive of a pill-induced injury, an autoimmune skin disease involving the esophagus, eosinophilic esophagitis or, less likely, a hypersecretory syndrome or a genotype that confers altered metabolism of PPIs. Refractory reflux syndromes associated with normal endoscopy findings are more problematic to diagnose and further testing may be required, including prolonged 48 h pH testing, impedance measurements (for nonacid reflux), esophageal manometry and gastric function tests. For patients with refractory GERD who do not have esophagitis, possible etiologies include nocturnal gastric acid breakthrough, nonacid GER, missed GER or other diseases such as achalasia, gastroparesis or functional heartburn.

KEYWORDS eosinophilic esophagitis, GERD, nonacid reflux, pill esophagitis, PPIs

CME

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Learning objectives
Upon completion of this activity, participants should be able to:
1. Identify the percentage of patients who do not respond to first-line treatment for gastroesophageal reflux disease (GERD).
2. Define refractory GERD.
3. Describe the most appropriate first step in the investigation of refractory GERD.
4. List most likely diagnoses that account for refractory GERD with esophagitis.
5. Identify appropriate tests for investigating refractory GERD after endoscopy.

INTRODUCTION
Medical therapy for GERD has improved remarkably since the introduction of PPIs in the late 1980s; however, some patients still do not respond as expected to the therapy currently available. Despite twice-daily dosing of PPIs, reflux symptoms can persist, new symptoms can occur or be unmasked, and esophagitis can fail to heal. Some patients with unresponsive GERD might not take their medications. The unresponsiveness of the disease might also be caused by nonacid reflux, or be contributed to by well-defined pharmacokinetic factors. In addition, the esophagitis and/or symptoms present might not be caused by acid reflux. Management of the difficult-to-treat ('refractory') reflux patient can, therefore, be a challenge for the clinician. This Review considers the initial treatment of patients with GERD, the diagnostic approach to refractory GERD, and the diagnoses possible in

patients with refractory GERD in the presence and absence of esophagitis.

DIAGNOSTIC APPROACH TO GERD REFRACTORY TO INITIAL TREATMENT

At present, patients who have GERD symptoms (i.e. heartburn and/or acid regurgitation) do not undergo initial endoscopy unless they have dysphagia, bleeding or weight loss. Instead, these patients are given a 4–8-week trial with a PPI to be taken in the morning before breakfast. Failure to respond to such a treatment trial occurs in 25–42% of patients, which classifies them as 'more difficult to manage'.[1] At this point, the physician should confirm patient compliance and check that the patient is taking the PPI dose at the recommended time (i.e. 30 min to 1 h before a breakfast meal). One study found that, in the US, nearly 70% of primary care physicians and 20% of gastroenterologists advised patients to take the PPI dose at bedtime or did not believe that the relationship to meals was important.[2]

When patient compliance and the correct timing of the PPI dose have been confirmed yet symptoms persist, it is reasonable to switch to use of a second-generation PPI. The efficacy of this approach was supported in a multicenter study of patients who had persistent heartburn despite receiving lansoprazole 30 mg in the morning before breakfast.[3] Switching patients to a single morning dose of esomeprazole 40 mg was as helpful as administering twice-daily lansoprazole 30 mg for the relief of heartburn symptoms during 8 weeks of treatment and was much less expensive. Nevertheless, most physicians instead introduce twice-daily dosing (before breakfast and dinner) of the same PPI, and up to 25% of patients respond.[4] Those who do no better after twice-daily dosing fall into the 'refractory GERD' category (Figure 1).

Upper endoscopy

In my experience, the first test that should be performed in patients with refractory GERD (if not done earlier) is upper endoscopy. Upper endoscopy can exclude the possibility that the patient has refractory peptic ulcer disease or, less likely, gastric cancer, and can identify the presence of 'acid-resistant' esophagitis. Although less common than nonerosive esophagitis, acid-resistant esophagitis represents several well-defined diseases that can be identified by careful history taking, by physical examination, and from blood test results. Esophageal pH testing
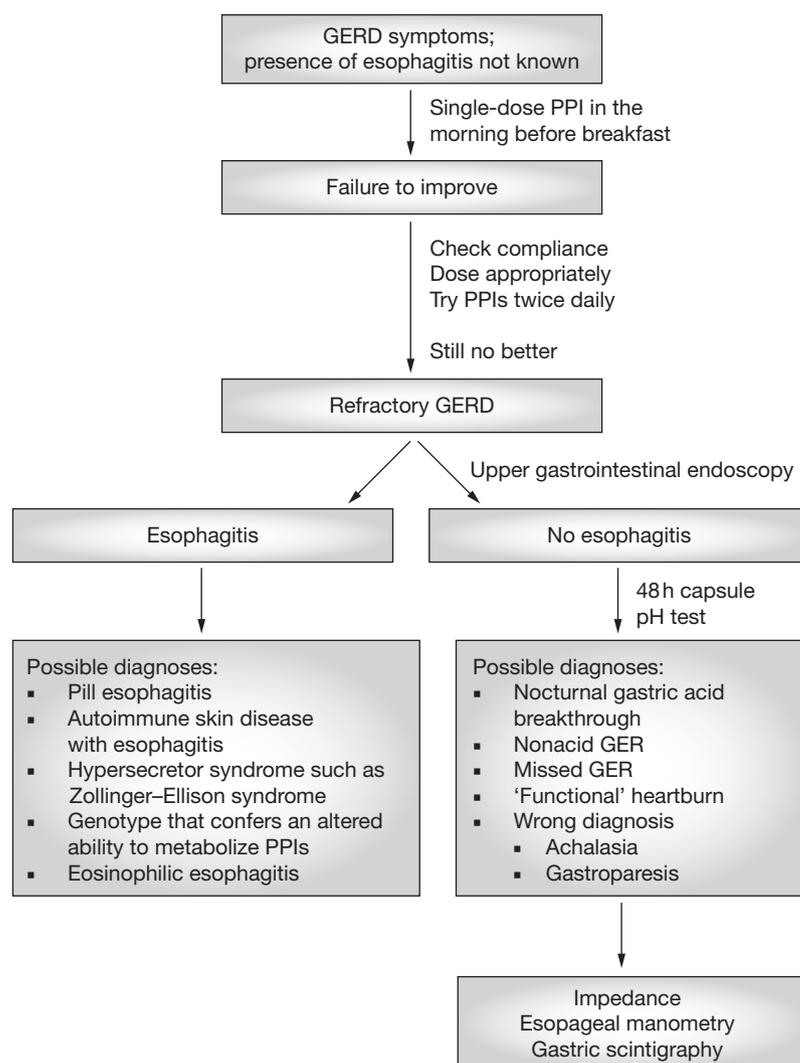

Figure 1 Algorithm used by the author for the management of patients with GERD. Abbreviation: GER, gastroesophageal reflux.

usually confirms that the patient on twice-daily PPIs has excellent acid control and supports a nonacid etiology for their esophagitis.[5]

During my time at the Cleveland Clinic, it was much more common for patients with refractory GERD to have normal rather than abnormal endoscopy findings (JE Richter, unpublished observations). I would say that patients with refractory GERD who have normal endoscopy findings account for approximately 90% of all patients with refractory GERD.

Esophageal pH testing

Esophageal pH testing is my next test of choice for patients with refractory GERD while on twice-daily PPI therapy. In the experience of

the Cleveland Clinic group, however, only 7% of patients on twice-daily PPI therapy who have classic heartburn symptoms and 1% of patients who have atypical reflux symptoms still have abnormal amounts of acid reflux.[5]

Although it is currently popular to suggest that patients with refractory GERD have nonacid GER, other diagnoses need to be considered that might be more common. For example, these patients could have 'missed' acid reflux that was not picked up on a single-day study (25% of cases monitored by capsule pH testing had normal findings one day and abnormal findings the next day in a 48 h study[6]), or the pH probe might be missing distal acid reflux confined to just above the esophogastric junction. Alternatively, patients with refractory GERD might have a nonreflux diagnosis such as achalasia, gastroparesis, or 'functional heartburn'. Currently available technology, such as impedance monitoring, capsule pH testing, esophageal manometry and/or gastric scintigraphy, might help us to identify many patients who have nonreflux disease.

REFRACTORY GERD WITH ESOPHAGITIS
Patients on twice-daily PPIs rarely have clinically important acid-induced esophagitis unless noncompliance is an issue or they have a hypersecretory syndrome, such as the Zollinger–Ellison syndrome. There are several diagnoses to consider in patients who have refractory GERD and esophagitis (Figure 1).

Pill-induced esophagitis
Pills can be a complicating factor in young or elderly patients.[7,8] In young patients, symptoms are acute and often associated with odynophagia, chest pain and dysphagia, as well as heartburn. In elderly patients, complaints can be chronic and complicating an underlying esophageal motility disorder or undiagnosed stricture.

Endoscopy may identify classic 'pill esophagitis', which is characterized by one or more discrete ulcers with normal surrounding mucosa. The presence of diffuse inflammation, thick whitish exudates, pseudotumors, fibrotic strictures and even perforation has also been reported. The most common site of pill-induced injury is the junction of the proximal and middle third of the esophagus, where peristaltic amplitude is relatively low and where the esophagus is compressed by the aortic arch. The distal esophagus may also be involved, sometimes with sparing of the squamocolumnar junction, which helps to differentiate pill esophagitis from reflux esophagitis.

Drugs commonly cited as a cause of pill esophagitis include doxycycline and tetracycline (especially in the young), alendronic acid, naproxen, potassium chloride, ascorbic acid, quinidine and ferrous sulphate. In one large series of patients with pill esophagitis,[8] A third of the cases were found to be caused by aspirin or NSAIDs. Most patients improve within 1 week of stopping taking the offending agent and starting treatment with PPIs and/or sucralfate. Patients who develop strictures may require dilatation.

Prevention is the key for the management of pill esophagitis. All patients, in particular the elderly, should take their pills with at least 0.24 l (8 fl oz) of water and not recline or go to bed within 1 h of taking any medication.

Autoimmune skin diseases
Various dermatologic diseases can involve the esophagus. The dermatologic diseases most likely to cause an intractable esophagitis syndrome are autoimmune diseases, including epidermolysis bullosa acquisita, pemphigus vulgaris, cicatrical pemphigoid, and lichen planus.[9] Patients with these diseases are usually middle-aged women and they often complain of dysphagia caused by proximal esophageal strictures; associated skin, oral mucosa and anogenital disease might not be obvious. Endoscopy reveals diffuse erythema, blistering of superficial mucosa (which peels easily away from the submucosa), whitish nodules or plaques and proximal stricture disease.[9] In some rare cases, a cast of the entire esophageal lining is vomited—so-called esophagitis dessicans superificialis.

When the esophagitis involves blistering of the mucosa, biopsy samples of involved and especially uninvolved esophageal mucosa should be obtained and sent for direct and indirect immunofluorescence testing to enable an accurate diagnosis to be made. In cases of suspected lichen planus, biopsy samples of the whitish nodules often reveal a dense histocytic infiltrate. Referral to a dermatologist should be made as these patients will require immunosuppressive therapy that includes prednisone, dapsone, azathioprine, cyclophosphamide or tacrolimus. Some patients require frequent esophageal dilation for the treatment of their stricture disease; intralesional injection of corticosteroids might also be helpful.[10]

Acid hypersecretion

Acid secretion is normal in patients who have GERD, and acid hyposecretion protects patients from GERD and its complications. On the other hand, 30–45% of patients with Zollinger–Ellison syndrome have endoscopically visible esophagitis, some with difficult-to-manage esophageal strictures.[11] When PPIs are administered (usually twice daily) to lower gastric acid secretion to <10 mEq/h, more than two-thirds of patients will have symptom reduction and healing of esophagitis.[11] Some patients who have recalcitrant strictures may need their gastric acid output reduced to <1 mEq/h to decrease the need for frequent esophageal dilation.[11] In one study, predictors for esophagitis in patients with Zollinger–Ellison syndrome included vomiting, low lower-esophageal sphincter pressure and obesity.[12]

Genotypic differences

PPIs are mainly metabolized by the hepatic cytochrome P450 2C enzymes. Although pharmacokinetic interactions at the cytochrome level are uncommon, there is considerable genetic variation among patients in the ability of their cytochrome P450 2C enzymes to metabolize PPIs. There have been reports that plasma concentrations of, and acid-inhibitory effects on, omeprazole and lansoprazole depend on the patient's *CYP2C19* (cytochrome P450, family 2, subfamily C, polypeptide 19) genotype.[13] Patients who are rapid metabolizers of PPIs have less lowering of gastric acidity and poorer rates of esophagitis healing than do slow or intermediate metabolizers.[13] This genetic pattern of rapid PPI metabolism is more common in the Asian population (12–20%) than in the white population (3–6%). One study suggests that, unlike other PPIs, esomeprazole might be preferentially metabolized through another pathway that is mediated by CYP3A4 and might, therefore, overcome this problem.[14] So far, all studies of genotypic differences in PPI metabolism have been done in patients receiving single doses of PPIs; it is not known whether twice-daily dosing will overcome the problem of rapid PPI metabolism.

Eosinophilic esophagitis

Eosinophilic esophagitis is an increasingly common diagnosis in patients with refractory GERD. Patients with eosinophilic esophagitis are usually young men, present with a history of intermittent solid food dysphagia, and often have a history of food impaction. Most of these patients carry an underlying diagnosis of GERD.[15–17] Many have associated asthma or food allergies, especially against milk, eggs, soy, peanuts or melons.

The diagnosis of eosinophilic esophagitis is suggested by endoscopic findings of multiple esophageal rings, longitudinal furrows, or pinpoint white exudates. Biopsies of the proximal and distal esophagus should be taken, and histology of the biopsy specimens will show >15–20 eosinophils per high-power field.[18] Peripheral eosinophilia is uncommon. The pathogenesis of eosinophilic esophagitis is unknown. Some data suggest that the condition is precipitated by foods and aeroallergens that stimulate a type 2 T-helper cell cytokine response,[19] whereas other data suggest that some patients have an atypical variant of GERD.[20,21] The natural history of eosinophilic esophagitis is poorly understood, but the condition has not been associated with esophageal cancer.[22]

Treatment of patients with eosinophilic esophagitis with inhaled steroids (e.g. fluticasone propionate twice daily [morning and evening]) for up to 3 months will reduce the number of eosinophils and improve symptoms.[23] To ensure adequate delivery of the steroid to the esophagus and not the lungs, a spacer should not be used with the inhaler. The patient should be instructed to inspire deeply and, at the same moment, depress the inhaler and swallow the aerosol. The patient should rinse their mouth out with water and avoid food or drink for 2–3 h. A randomized, placebo-controlled trial published in 2006 found that fluticasone propionate (440 μg twice daily) was more effective than an identical placebo over 3 months for the induction of histologic remission of eosinophilic esophagitis.[24] This was, however, a pediatric study and no placebo-controlled studies performed in adults have yet been published.

If inhaled steroids fail to resolve symptoms, other therapies include a leukotriene D_4 antagonist (montelukast 10–40 mg per day) or oral steroids (prednisone 30 mg per day for 2 weeks and taper over 6 weeks). Oral candidiasis can complicate steroid therapy.[23] Other patients do well with PPIs and careful bougie dilation.[20]

REFRACTORY GERD WITHOUT ESOPHAGITIS

The most common endoscopic finding in patients with refractory GERD is a normal esophagus, often without a hiatal hernia. For these patients, making a diagnosis is much more problematic and less likely to lead to a satisfactory outcome.

In the experience of the Cleveland Clinic group, patients with refractory GERD but no esophagitis who are on PPIs twice daily have a less than 10% chance of having an abnormal esophageal reflux profile.[4] This means that a diagnosis of nonacid GER, missed GER or functional heartburn needs to be considered. These diagnoses are, however, limited by the lack of treatment alternatives and clear understanding of their clinical relevance based on current technology used to study these syndromes. Other potential etiologies such as achalasia and gastroparesis should always be evaluated and excluded (Figure 1).

Nocturnal gastric acid breakthrough
Persistent gastric acidity at night despite therapy with PPIs twice daily is common (60–80% of patients) and is probably important for protecting the gastrointestinal tract from bacterial contamination and the action of nitrosamines.[25] This natural phenomenon means, however, that there is the potential for breakthrough acid reflux at night—so-called nocturnal gastric acid breakthrough (NAB)—when the esophagus is least protected.

One study in healthy volunteers found that NAB was nearly eliminated by the addition of histamine-2-receptor antagonists (H_2RAs; ranitidine 150 mg or 300 mg at bedtime) to omeprazole 20 mg twice daily.[25] Another study that tried to replicate these findings in 40 individuals (20 healthy volunteers and 20 patients with GER) found identical results after 1 day when a bedtime H_2RA was added to a twice-daily PPI regimen; however, after one week and four weeks, the night-time gastric acid exposure had returned to values observed with PPIs alone.[26] This loss of control of NAB is secondary to the development of tolerance to H_2RAs, which frequently occurs with continuous usage for longer than 1 week.[27] Although it has not been formally tested, intermittent use of H_2RAs when a patient is exposed to refluxogenic stimuli (e.g. after eating a large fatty meal or a night drinking cocktails) might be the optimal approach to minimizing the likelihood of developing drug tolerance.

Nonacid gastroesophageal reflux
New technology permits the measurement of nonacidic reflux (often erroneously mislabeled as bile reflux) when a patient is in an ambulatory state. Impedance testing measures the movement of liquids and gases in the esophagus; combined with pH testing, it can identify nonacid reflux. Most nonacid reflux, especially when patients are on PPI therapy, is actually weakly acidic (pH 4.0–6.5) and occurs during the daytime.[28] The Bilitec® recorder (Alpine Biomed Corp., Fountain Valley, CA) measures reflux of bilirubin, a surrogate for bile reflux, and bile reflux probably accounts for only 10–15% of nonacid reflux.[29] Studies of patients on PPIs twice daily suggest that 20–40% of patients have nonacid reflux, which may be contributing to their persistent symptoms.[30–33] Among the impedance studies,[32,33] the low side of the range (i.e. ~20%) represents individuals who have abnormal quantities of nonacid reflux, whereas the higher values (i.e. ~40%) are obtained through the inclusion of patients who have a positive symptom relationship (symptom index or symptom association probability), usually without pathological amounts of nonacid reflux. Although one study found that baclofen (5 mg three-times daily increased slowly to 20 mg three-times daily) decreases duodenogastro-esophageal reflux and improves symptoms, little long-term efficacy or safety data are available.[34] Other than for the treatment of clear symptoms of regurgitation, the role of antireflux surgery in nonacid reflux has not been carefully studied.

Missed gastroesophageal reflux
Acid GER can be missed by traditional pH catheters because it does not occur every day, the pH probe is placed too proximal in the esophagus, or the noxious effect of the nasal catheter limits eating and activity and results in a false-negative test. Wireless pH monitoring (Bravo™ capsule, Medtronics, Minneapolis) enables acid reflux to be measured for a period of at least 2 days. On the basis of initial studies with the wireless system, at least 25% of patients do not experience reflux on two consecutive days.[6] The Bravo™ capsule also enables the pH to be monitored in unusual situations (e.g. during heavy exercise or while swimming) and can potentially collect pH data until the capsule dislodges (usually after 5–7 days), as long as the data are downloaded every 48 h and the batteries are changed.

Traditionally, the pH probe is placed 5 cm above the proximal border of the lower esophageal sphincter, despite the interesting observation that reflux esophagitis rarely extends this far proximal to the esophagogastric junction. One study found that over a period of 24 h, the amount of acid exposure in 11 endoscopy-negative dyspeptic patients was greater 5 mm

above the squamo-columnar junction than when measured the conventional 5 cm above the squamo-columnar junction (11.7% vs 1.8%; $P<0.001$).[35] Whether missed acid reflux in patients on twice-daily PPIs contributes to the intractable symptoms of refractory GERD is unknown at this time.

Functional heartburn

Functional heartburn is defined as episodic retrosternal burning in the absence of pathological GER, motility disorders or structural abnormalities.[36] Patients with functional heartburn are frequently young, are usually nonobese and are predominantly women.[37]

Among untreated patients who have heartburn and normal endoscopy findings, 30–50% have normal 24 h pH test results, thus meeting the criteria for functional heartburn.[38] The results of two impedance studies published in 2006[32,33] indirectly imply that 50–60% of symptomatic patients who are on twice-daily PPIs have no symptom correlation with either acid reflux or nonacid reflux. The functional heartburn group, therefore, accounts for most of the patients with GERD who are refractory to PPI therapy. Visceral hyperalgesia is the main mechanism underlying functional heartburn, on the basis of the findings of balloon distension and esophageal-evoked-potential studies.[39] Higher doses of PPIs or antireflux surgery are not the answers for these patients; rather, they need treatment with pain modulators such as tricyclic antidepressants and selective serotonin reuptake inhibitors.[38]

Wrong diagnosis

Achalasia in the presence of a minimally dilated esophagus can mimic GERD. Patients with achalasia complain of heartburn as well as dysphagia, with the latter responding poorly to bougie dilation. Achalasia can easily be diagnosed by a barium esophagram and esophageal manometry.

Patients who have epigastric pain, early satiety, post-prandial abdominal bloating, nausea and vomiting may have delayed gastric emptying that is contributing to or worsening their reflux disease. I find delayed gastric emptying a common problem (10–20% incidence) in patients with difficult-to-manage reflux symptoms for whom regurgitation rather than heartburn is their major complaint.[40] In my clinical experience, a low-fiber diet and prokinetics often help decrease these patients' PPI requirements.

CONCLUSIONS

Patients who have refractory GERD should first undergo upper endoscopy to exclude peptic ulcer disease and cancer and to identify the presence of esophagitis. Refractory esophagitis suggests that they have a pill injury, an autoimmune skin disease with associated esophageal involvement, or eosinophilic esophagitis. Less likely causes of their symptoms are a hypersecretory syndrome (e.g. Zollinger–Ellison syndrome) or a genotype that confers an altered ability to metabolize PPIs.

Refractory reflux syndromes in patients who have normal endoscopy findings are more problematic to manage. These patients have to undergo further testing, including the measurement of nonacid reflux, prolonged pH monitoring for 48 h or more, esophageal manometry, and gastric function tests. Although making a diagnosis of nonacid reflux is currently popular, the appropriate medical and surgical treatments for nonacid reflux are poorly defined. Atypical presentation of achalasia and gastroparesis should also not be overlooked in patients who have refractory reflux syndromes and normal endoscopy findings; however, most of these patients have functional heartburn caused by visceral hyperalgesia.

KEY POINTS

- Approximately 25% of patients who have reflux symptoms fail to respond to twice-daily PPI treatment for 4–8 weeks; these patients are said to have 'refractory GERD'

- The first test to perform in patients with refractory GERD is upper endoscopy, primarily to assess the presence or absence of esophagitis and other gastric pathology

- Patients who have esophagitis most commonly have pill-induced injury, autoimmune skin disease associated with esophageal involvement, or eosinophilic esophagitis

- Those patients who do not have esophagitis are more problematic to manage and have to undergo further tests, including prolonged pH monitoring, impedance testing for nonacid gastroesophageal reflux (GER), esophageal manometry or gastric function testing

- Patients with refractory GERD without esophagitis might have nocturnal acid breakthrough, nonacid GER or missed acid GER, functional heartburn, or another disease such as achalasia or gastroparesis

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