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Refractory Gastro-Oesophageal Reflux Disease

Diagnosis and Management

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Contents

Abstract

Refractory gastro-oesophageal reflux disease (GORD) is described when reflux symptoms have not responded to 4–8 weeks of proton pump inhibitor therapy and occurs in a heterogeneous mixture of patients. The causes of refractory GORD include inadequate acid suppression, non-acid gastro-oesophageal reflux, and non-reflux causes of GORD symptoms including achalasia, gastroparesis and functional heartburn. Upper gastrointestinal tract endoscopy should initially be performed to identify the presence of oesophagitis, and exclude other diagnoses including eosinophilic oesophagitis and peptic ulcer disease. Patients with refractory symptoms but with a normal upper endoscopy are more difficult to diagnose and may require ambulatory pH monitoring, impedance testing, oesophageal motility tests and gastric emptying scans. The primary goal of treatment is symptom reduction and eventual elimination, which can be achieved with proper identification of the underlying cause of the symptoms.

Gastro-oesophageal reflux disease (GORD) is defined as symptoms or tissue injury due to abnormal reflux of gastric contents into the oesophagus, and is the most expensive digestive disease.[1] Studies have identified the prevalence of GORD to be 10–20% of the population.[2] Severe

GORD is also a major risk factor for oesophageal adenocarcinoma,[3] which is the cancer with the fastest growing incidence in the US.[4] GORD occurs as a result of dysfunction of the anti-reflux barrier at the oesophago-gastric junction; this barrier is anatomically and physiologically complex and vulnerable to a number of potential mechanisms of reflux. The two main patterns of lower oesophageal sphincter (LOS) dysfunction are hypotensive LOS and pathological transient inappropriate LOS relaxations.[5,6]

The primary symptom of GORD is heartburn, a retrosternal burning discomfort located in the epigastric area, which may radiate upwards towards the neck. Atypical manifestations of GORD refer to those symptoms that are extra-oesophageal (pulmonary or ear, nose and throat [ENT] manifestations) in origin, or symptoms that are oesophageal in nature but are not typical GORD symptoms (e.g. non-cardiac chest pain). ENT manifestations include reflux laryngitis and globus; pulmonary manifestations include chronic cough, asthma and aspiration pneumonia.

The mainstay of medical treatment for GORD consists of acid suppression. The most potent pharmacological agents for GORD are the proton pump inhibitors (PPIs). The PPIs act by blocking the H^+/K^+-adenosine triphosphatase (ATPase) on the apical surface of the parietal cells in the stomach. PPIs are usually given either once or twice daily and are typically well tolerated. Adverse effects have been reported in up to 5% of patients, the most common being headaches and diarrhoea.

There is no consensus definition of refractory GORD, but the term usually implies continued reflux symptoms after at least 4–8 weeks of twice-daily PPI therapy.[7,8] Surveys of GORD patients receiving PPI therapy show that 25–42% of patients are refractory to a once-daily PPI, of which 25% would respond to an increase in PPI dosing to twice daily.[9,10] However, 42% of GORD patients are dissatisfied with their PPI treatment outcomes.[11] Although, this survey did not determine the cause of PPI failure, the percentage of GORD patients with refractory symptoms may be substantial. In general, patients with refractory GORD can be classified as either patients who require more aggressive medical therapy (more medications, better compliance with medications or optimal timing) or patients who have other non-reflux causes of their symptoms (table I).

Table I. Causes of refractory gastro-oesophageal reflux (GORD)

Acid reflux related
Non-compliance
Inadequate dosing or timing
Rapid proton pump inhibitor metabolism
Nocturnal acid breakthrough
Zollinger-Ellison syndrome
Non-GORD conditions
Eosinophilic esophagitis
Pill esophagitis
Infectious esophagitis
Candida albicans
cytomegalovirus
herpes simplex virus
Dermatological disorders
epidermolysis bullosa acquisita
pemphigus vulgaris
cicatrial pemphigoid
lichen planus
Motility disorders
achalasia
diffuse oesophageal spasm
Gastroparesis
Functional heartburn

For patients with refractory GORD, there is no standardized management algorithm and this can be a challenge for the clinician. The primary goal of treatment is symptom reduction and eventual elimination, which can be achieved by stepwise assessment and management in most patients.

1. Initial Evaluation

The primary symptoms of GORD are heartburn and regurgitation. In patients with typical symptoms who respond to medical therapy, no further testing is needed. Patients with symptoms consistent with GORD but who do not respond to a trial with a PPI taken before breakfast are usually tried on a twice-daily PPI

dose (before breakfast and dinner). Failure to respond to a 4- to 8-week trial of high-dose PPIs indicates refractory GORD (an 8-week trial will allow most patients to respond). In these patients, a detailed history should be obtained to determine the presence of the alarm symptoms of dysphagia, gastrointestinal (GI) bleeding (overt or occult) and weight loss. Physical examination of these patients should exclude the presence of any epigastric mass or signs of GI bleeding.[12,13]

Patient compliance with both the dosing and timing of PPI therapy needs to be assessed, as this is the most common cause for refractory symptoms of GORD. Patients should be instructed to take their PPIs 30 minutes prior to breakfast and dinner, as PPIs only affect actively secreting ATPase, which are transported to the surface of the parietal cell only after the intake of a meal. However, in one survey 70% of primary care physicians did not fully understand the importance of timing of PPIs to meals and hence prescribed the drug to be taken at inappropriate times.[14] Additionally, one study found that as many as 45% of GORD patients did not take their once-daily PPIs as prescribed during a 4-week period.[15] Although for many patients with GORD the timing of PPI ingestion has little influence on clinical response, there is substantial individual variability and for patients with refractory GORD symptoms proper timing of PPIs is important. In the absence of any worrisome signs and symptoms, a non-compliant patient should be reassessed after a 4- to 8-week period of taking their PPI medication at the prescribed times.

If a patient is taking twice-daily PPI therapy, at least one meal (breakfast or lunch) should be ingested before the evening dose to ensure that there are maximal possible numbers of ATPase binding sites available. The optimal timing of the evening dose is before dinner. No significant therapeutic benefit has been identified between different formulations of PPIs for refractory GORD, albeit individual patients may experience varying responses and adverse effects while receiving different PPIs.[12] Switching between PPIs may be appropriate in situations of intolerance to a PPI.

2. Diagnostic Approach

2.1 Anatomic Assessment: Endoscopy

The goal of diagnostic testing for refractory GORD patients is to determine the underlying cause(s) of the symptoms and to exclude the presence of other serious diseases that can mimic reflux symptoms. The value of upper GI endoscopy in patients whose PPI treatment failed has not been adequately studied. Overall, most patients will have a normal endoscopy. However, upper GI endoscopy can reveal an alternative diagnosis and is needed clinically to sort out the underlying cause of the symptoms. A number of potential causes for refractory GORD symptoms can be determined with an upper GI endoscopy. Oesophagitis of various causes, oesophageal strictures, gastric ulcers, and even oesophageal and gastric cancers can all present with symptoms similar to GORD. Non-reflux causes of oesophagitis include eosinophilic oesophagitis, pill-induced oesophagitis, infectious oesophagitis and autoimmune disorders.

Eosinophilic oesophagitis is a chronic disorder that commonly presents in young adults aged between 20 and 40 years. Eosinophilic oesophagitis is predominantly identified in males (80%). Patients typically present with dysphagia and often food impaction, and may have reflux symptoms. Eosinophilic oesophagitis is increasingly being recognized in adults, although historically the condition was under-recognized and often confused with GORD.[16] Although the aetiology is unknown, asthma and allergic conditions have been associated with eosinophilic oesophagitis, including food allergies, commonly to milk, soy, eggs, melons or peanuts.

Biopsies of the mid and distal oesophagus should be taken at the time of endoscopy if the appearance of the oesophagus does not suggest GORD to exclude the presence of eosinophilic oesophagitis. For the diagnosis of eosinophilic oesophagitis, five mucosal biopsies from at least two levels are needed for histology.[17] The presence of more than 15–20 eosinophils per high-power field in biopsies is generally considered sufficient evidence to diagnose eosinophilic oesophagitis.

Treatment of eosinophilic oesophagitis consists of the topical corticosteroid fluticasone propionate twice daily (without a spacer), to be swallowed and not inhaled. It is recommended that the patients rinse their mouths after swallowing the corticosteroids to reduce the potential for development of oral candidiasis, and to avoid eating or drinking for 2–3 hours afterwards. Other therapeutic agents such as the leukotriene D_4 receptor antagonist montelukast (at 10–40 mg/day) or oral corticosteroids (prednisone starting at 30 mg/day for 2 weeks and then tapering the dose over 6 weeks) can be used if topical fluticasone propionate is not successful.

Pill-induced oesophagitis is especially common in the elderly or patients taking certain types of medications.[18] Medications that can cause oesophagitis include alendronate, antibacterials, aspirin, iron salts, NSAIDs, potassium chloride, quinidine and theophylline. More than 50% of pill-induced oesophagitis is due to tetracycline and related medications, especially doxycycline. There are various mechanisms by which pills induce oesophageal damage, including prolonged contact time with the oesophageal mucosa and pill acidity. Commonly, pills get stuck at sites of anatomic narrowing, such as the arch of the aorta and the distal oesophagus. Factors that increase the risk of pill-induced oesophagitis are advancing age, swallowing position, fluid intake and pill size. Position may be the most important risk factor for oesophageal injury, as medications ingested while supine with insufficient fluids may remain in the oesophagus for up to 90 minutes. The mainstay of treatment for pill-induced oesophagitis is to identify and avoid the offending drug. If possible, liquid forms of medication should be used. Medications should be administered with at least eight ounces of fluids and patients should remain in an upright position for a minimum of 30 minutes after swallowing pills.

Infectious aetiologies of oesophagitis are not uncommon in immunocompromised patients, including those who are post-transplant or taking corticosteroids, those with cancer who are receiving chemotherapy, and those with diabetes mellitus, alcoholism or HIV infection. Patients with infectious oesophagitis typically have odynophagia, but may present with heartburn, dysphagia, fever, nausea or bleeding. The three most common causes of infectious oesophagitis are *Candida albicans*, cytomegalovirus (CMV) and herpes simplex virus (HSV). Of these, the most frequent cause of infectious oesophagitis is *C. albicans*. Infection of the oesophagus with CMV often occurs as part of a generalized GI CMV infection in immunocompromised patients. HSV oesophagitis can occur in both immunocompetent and immunocompromised hosts; in immunocompetent hosts, this usually is from reactivation of a latent infection but may be from primary HSV.

Although uncommon, certain autoimmune dermatological diseases can also involve the oesophagus, and have been reported to cause refractory oesophagitis including epidermolysis bullosa acquisita, pemphigus vulgaris, cicatricial pemphigoid and lichen planus.[19] The typical patient is a middle-aged woman who has a proximal oesophageal stricture; the skin manifestations may or may not be prominent. The endoscopic appearance of the oesophagus in these conditions is variable and may include diffuse erythema, blistering superficial mucosa that easily peels away from the submucosa, whitish nodules and plaques, and proximal stricturing disease. Endoscopic biopsies should be obtained from both the involved and uninvolved areas of the oesophagus, and sent for both direct and indirect immunofluorescence testing. Treatment of these patients is usually in conjunction with a dermatologist, with immunosuppressive agents as the primary therapy including prednisone, azathioprine, dapsone, tacrolimus and cyclophosphamide. For patients with strictures, oesophageal dilations and intra lesional triamcinolone injections have been used.[20]

The presence of persistent reflux oesophagitis with or without gastric/duodenal ulcers in patients receiving PPI therapy should raise suspicion for increased gastric acid production and the possible diagnosis of Zollinger-Ellison syndrome. Oesophagitis in these patients may be difficult to manage because of the gastrinoma-induced hypersecretion of acid in the stomach.[19] In Zollinger-Ellison syndrome, low LOS pressure, vomiting and obesity are predictors of

oesophagitis.[21] Localization of the gastrinoma with resection if possible and aggressive acid reduction are the mainstays of treatment for Zollinger-Ellison syndrome patients.

Another explanation for persistent reflux oesophagitis in patients receiving PPI therapy is the rapid metabolism of PPIs. The hepatic cytochrome P450 (CYP) 2C19 isoenzyme is principally responsible for the metabolism of PPIs, and there is substantial genetic variation among patients in this enzyme activity level. Patients with rapid metabolism of PPIs have poorer rates of oesophageal healing and less normalization of gastric pH than most patients (who are low or intermediate metabolizers). Rapid PPI metabolism is more common in Asian populations (12–20%) than in Caucasian populations (3–6%).[22] There are rare patients who have PPI resistance, presumably caused by mutations in the proton pump, who respond to treatment with histamine H_2 receptor antagonists.

2.2 Functional Evaluations

2.2.1 Ambulatory Oesophageal pH Tests

In the majority of patients with refractory GORD, endoscopy will be normal, and an ambulatory oesophageal pH test should be considered the next step. Ambulatory pH monitoring has traditionally been the gold-standard test for the diagnosis of GORD. This test is performed by placing a small catheter into the distal oesophagus via the nares and leaving it in place for 24 hours. For patients whose symptoms are atypical for GORD or if there is any question of the diagnosis of GORD, a pH test should be performed while the patient is not receiving medical therapy to confirm the diagnosis of GORD. What is important in those with an abnormal pH result while not taking medications is the symptom index and symptom association probability that identifies heartburn episodes associated with reflux. The symptom index is considered positive if it is >50% and symptom association probability is considered positive if it is >95%. For most patients with typical reflux symptoms or with a known diagnosis of GORD from previous pH testing or findings of erosive oesophagitis on upper GI endoscopy, the pH test can be performed while they are receiving PPI therapy to evaluate for adequate acid suppression. A non-acid aetiology is commonly found in these patients as pH testing usually shows excellent control with twice-daily PPIs.

Traditional pH monitoring studies have been hampered by the potential for a lack of symptomatic events during the 24-hour recording period. A more prolonged study time of 48 hours with the recently available wireless pH capsule can detect more abnormal oesophageal acid exposure, which increases the yield of the test.[23] The wireless pH capsule is useful in assessing for the presence of GORD in patients not receiving PPI therapy or for adequacy of acid suppression in patients receiving PPI therapy. In situations where there is an excess of acid reflux measured, the dose of the acid suppressor may need to be adjusted accordingly. Incorrect dosing (rather than resistance to medications) is a common occurrence in situations of refractory GORD.[12]

2.2.2 Multi-Channel Intraluminal Impedance Testing

Multi-channel intraluminal impedance (MII) testing is a relatively new test of oesophageal function. MII testing was introduced to quantitatively determine the amount of solid, liquid and air reflux over a 24-hour period. It has become the preferred method when available for the evaluation of patients with refractory GORD symptoms as it can detect weakly acidic (pH of 4.0–6.5) and non-acidic reflux.[12] The catheter has two sets of sensors: electrical sensors for the detection of non-acid reflux (air and solids) and pH sensors for the detection of acid reflux. With MII testing, several studies showed that 20–40% of patients receiving twice-daily PPI therapy have non-acid reflux.[24,25] In patients with non-acid reflux, when reflux pH values are non-acidic, the patient may benefit from Bilitec® testing (Alpine Biomed Corp., Fountain Valley, CA, USA) to measure the bilirubin concentration of the refluxate to ascertain if it is duodenal in origin. In patients with measurable duodenal reflux, evidence supports the concomitant use of prokinetic drug therapy and PPIs.[26,27] Duodenogastro-oesophageal reflux is purported to occur in as many as 25% of adult patients and

68% of paediatric patients who have refractory GORD.[27,28]

2.2.3 Oesophageal Manometry

Assessment of oesophageal motility is an important diagnostic tool to evaluate the position and function of the LOS. The function of the oesophagus and the LOS can also be assessed to evaluate for possible motility disorders, such as achalasia and diffuse oesophageal spasms.[12] Achalasia, when it presents with a normal or minimally dilated oesophagus, can mimic GORD and easily be diagnosed with oesophageal manometry. Despite having an elevated LOS pressure, patients with achalasia may paradoxically have heartburn symptoms due to bacterial fermentation of retained food in the oesophagus and production of lactate.[29] Diffuse oesophageal spasm, although it commonly presents with atypical chest pain, can also present with predominantly GORD symptoms.

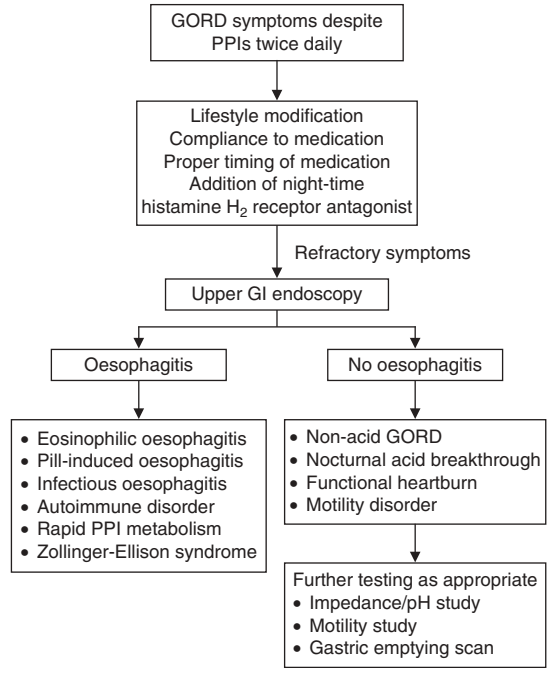

Fig. 1. Management algorithm for patients with refractory gastro-oesophageal reflux disease (GORD). **GI** = gastrointestinal; **PPIs** = proton-pump inhibitors.

3. Medical Management of Refractory Gastro-Oesophageal Reflux Disease (GORD) Symptoms

Refractory GORD occurs in a mixture of patients with gastroparesis, oesophageal motility disorders, oesophageal hypersensitivity and severe reflux disease that have not completely responded to anti-secretory agents. In all GORD patients, particularly those with refractory GORD, we recommend lifestyle modifications. Patients are encouraged to avoid foods that can exacerbate their symptoms of GORD. Smaller, more frequent meals and avoiding lying down for 2–3 hours after eating are strongly recommended. Elevating the head of the bed by six inches (blocks underneath the front feet of the bed) is also helpful, particularly for those with nocturnal symptoms. Smoking cessation and weight reduction may be very helpful in the resolution of GORD symptoms,[30] although this may be difficult to achieve for many patients. The current epidemic of obesity may increase the burden of disease in the coming years. Clinical evidence supporting the therapeutic benefits of these lifestyle modifications is somewhat limited, except in a select subset of patients.[31]

Patients with refractory GORD receiving twice-daily PPIs with no alarm symptoms should be considered for a stepwise medical management approach (figure 1). The first additional agent for nocturnal acid reflux is an H_2 receptor antagonist given before bedtime.[32] Nocturnal acid reflux despite twice-daily PPIs is common and is the cause of nocturnal gastric acid breakthrough. Episodes lasting >60 minutes of gastric acid with a pH <4.0 have been noted to occur in up to 70% of patients.[33] The use of an H_2 receptor antagonist is effective in relieving persistent nocturnal reflux symptoms in up to 25% of patients. The benefit of an H_2 receptor antagonist may diminish with time, as tolerance can develop after continuous usage for more than 1 week.

If a patient's symptoms do not respond to bedtime H_2 receptor antagonists, the next step is to perform an upper endoscopy if this has not already

been done to evaluate for other causes of symptoms. Patients with alarm symptoms first need to undergo evaluation with an upper GI endoscopy. If the upper GI endoscopy is negative, an oesophageal pH test or, if available, MII testing can be done to evaluate for persistent reflux. MII testing will answer the following key questions: (i) whether the patient has any GORD; (ii) whether the reflux, if present, is acidic; and (iii) whether the reflux, if present, is weakly acidic or non-acidic reflux. If MII is not clinically available and pH tests are available, either catheter-based or the wireless pH capsule (see section 2.2.1), testing the patient receiving PPI therapy will evaluate for persistent acid reflux as the cause of residual symptoms.

For management of patients with non-acid reflux, baclofen (5–20 mg three times daily) can help symptoms of regurgitation by decreasing transient LOS relaxations, although long-term efficacy data are not available.[34] There may be significant adverse effects with the use of baclofen, particularly drowsiness. A number of other agents are under development, but currently baclofen is the only agent available for clinical use that reduces LOS relaxation. Although there are no published studies on the use of bile acid-binding protein modulators (e.g. cholestyramine), we have used them to reduce GORD symptoms with varying degrees of success.

A common non-reflux aetiology for refractory GORD symptoms is delayed gastric emptying (gastroparesis), which occurs in up to 20% of patients with refractory GORD.[7] These patients may have refractory GORD symptoms (especially regurgitation) in association with nausea, early satiety and bloating. In centres with available solid-phase gastric emptying studies, the test should be performed prior to initiation of prokinetic therapies, which include erythromycin, metoclopramide and domperidone. However, if a solid-phase gastric emptying test is not readily available, a diagnostic/therapeutic trial of prokinetic agents can be offered to the patient, along with dietary modifications including frequent, small-volume, low-fat meals and a low-fibre diet.

Functional heartburn with episodic retrosternal burning in the absence of pathological gastro-oesophageal reflux is a poorly described syndrome that is likely to represent a combination of oesophageal hypersensitivity (visceral hyperalgia) and psychological co-morbidity. Functional heartburn may occur in the presence of other functional bowel disorders, such as irritable bowel syndrome.[26] Most patients with functional heartburn are not obese and are young females. These patients do not respond to increasing doses of PPIs and often need treatment with medications that modify pain perception, such as tricyclic antidepressants and selective serotonin uptake inhibitors.

4. Surgical and Endoscopic Treatment for Refractory GORD

Anti-reflux procedures aimed at augmenting the LOS, either surgically or endoscopically, is an aggressive approach for refractory GORD.[35] It is critical to determine that the refractory GORD symptoms are attributable to reflux before proceeding with a mechanical treatment option. The best outcomes are in young patients with typical GORD symptoms who require a high dose of medications for control of the symptoms. In patients whose symptoms fail to be controlled by therapy with PPIs, the response rates to surgery are much lower. Patients whose symptoms fail to respond to high-dose PPIs often have other non-reflux disorders that are responsible for their symptoms and, therefore, may not respond to a mechanical treatment.

Anti-reflux surgery has been performed since the early 1950s. The most widely performed procedure is laparoscopic Nissen fundoplication. The goal of anti-reflux surgery is to mechanically restore the normal oesophageal gastric junction via an open (transthoracic or transabdominal) or laparoscopic approach. These mechanical therapies attempt to reconstruct the physiological equivalent of normal LOS function and by doing so result in normalized reflux parameters.[36] Other procedures, such as Hill's, Belsy and Toupe repairs, have all been devised to offer anti-reflux surgical options for specific patient populations. For open fundoplication procedures, symptomatic response in typical GORD patients of 80–90% have been reported at 10-year follow-up.[37] For laparoscopic

fundoplication, a similar success rate of 85–90% has been reported.[38-40] When patients are carefully selected, control of symptoms at 10-year follow-up after surgery can be as high as 90%. However, response rates for surgery in patients with refractory GORD have been reported in a small series to be as low as 10%.[41]

Complications following fundoplication surgery include dysphagia,[42,43] chest pain, gas-bloat syndrome, post-operative hyperflatulence, and vagal nerve injuries leading to gastroparesis and diarrhoea. The prevalence of post-operative complications ranges from 5% to 20%.[44] Early post-operative dysphagia can occur in up to 18% patients, while late dysphagia can occur in 6% of patients at 2 years.[45] For those patients who do not respond to fundoplication initially, a second anti-reflux surgery can be performed. However, if the second fundoplication fails, there is no benefit with additional surgery.

Advances in endoscopic technologies have introduced innovative therapeutic options for GORD. Since 2000, the US FDA has approved five endoscopic devices for clinical use. These treatment modalities can be categorized into three groups: (i) radiofrequency ablation;[46] (ii) injectable bulking materials; and (iii) suturing of the gastroesophageal junction.[47] These procedures potentially offer a non-surgical alternative to patients with GORD. Of the three treatment groups, endoscopic suturing of the oesophageal gastric junction appears to have the best safety profile,[46-48] while the injectable polymer was recently withdrawn from the market because of safety concerns. Endoscopic suturing of the oesophageal gastric junction seems to be a safe procedure, with excellent initial clinical response rates in typical GORD of 70–80%.[49] However, endoscopic suturing has disappointing 2-year follow-up results, with only 25–40% of patients reporting complete symptomatic resolution.[50,51] Further improvements may require a better understanding of the underlying anti-reflux mechanism(s) of the endoscopic procedure and a more durable endoscopic therapy.

5. Conclusion

Refractory GORD management remains a challenge for physicians despite recent advances in diagnosis and therapy. There is substantial overlap of refractory GORD due to oesophageal reflux with other disorders presenting as refractory GORD symptoms. Initial diagnostic evaluation with upper GI endoscopy should aim at determining the presence of oesophagitis (reflux or other types). Additional studies to characterize the reflux contents and oesophageal function are helpful in defining the underlying aetiology of the refractory symptoms, including ambulatory pH tests, impedance testing, oesophageal manometry and gastric emptying scans. Non-reflux causes, such as gastroparesis and functional heartburn/oesophageal hypersensitivity, should be considered in patients with no identifiable aetiologies by any of the oesophageal diagnostic tests. The goal of medical management for refractory GORD is symptom reduction and eventual elimination. Medical therapy may be helpful in the management of patients with refractory GORD symptoms. Mechanical augmentation of the LOS via surgical or endoscopic approaches may provide significant symptom relief for carefully selected patients with documented GORD who respond to high doses of medications.

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References

1. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. Gastroenterology 2002; 122 (5): 500-11
2. Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2005 May; 54 (5): 710-7
3. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux is a strong risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825-31
4. Shaheen NJ. Advances in Barrett's esophagus and esophageal adenocarcinoma. Gastroenterology 2005 May; 128 (6): 1554-66
5. Dent J, Dodds WJ, Friedman RH, et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. J Clin Invest 1980 Feb; 65 (2): 256-67

6. Dodds WJ, Dent J, Hogan WJ, et al. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med 1982 Dec 16; 307 (25): 1547-52
7. Richter JE. How to manage refractory GERD. Nat Clin Pract Gastroenterol Hepatol 2007 Dec; 4 (12): 658-64
8. Fass R, Sifrim D. Management of heartburn not responding to proton pump inhibitors. Gut 2009 Feb; 58 (2): 295-309
9. Bardhan KD. The role of proton pump inhibitors in the treatment of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1995; 9 Suppl. 1: 15-25
10. Martinez SD, Malagon IB, Garewal HS, et al. Non-erosive reflux disease (NERD): acid reflux and symptom patterns. Aliment Pharmacol Ther 2003 Feb 15; 17 (4): 537-45
11. Crawley JA, Schmitt CM. How satisfied are chronic heartburn sufferers with their prescription medications? Results of the patient unmet needs survey. J Clin Outcomes Manage 2000; 7 (11): 29-34
12. Kahrilas PJ, Shaheen NJ, Vaezi MF. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. Gastroenterology 2008 Oct; 135 (4): 1392-413, 413 e1-5
13. Vakil N, Moayyedi P, Fennerty MB, et al. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. Gastroenterology 2006 Aug; 131 (2): 390-401; quiz 659-60
14. Barrison AF, Jarboe LA, Weinberg BM, et al. Patterns of proton pump inhibitor use in clinical practice. Am J Med 2001 Oct 15; 111 (6): 469-73
15. Gallup study of consumers' use of stomach relief products. Princeton (NJ): The Gallup Organization, 2000
16. Sgouros SN, Mantides A. Refractory heartburn to proton pump inhibitors: epidemiology, etiology and management. Digestion 2006; 73 (4): 218-27
17. Gupte AR, Draganov PV. Eosinophilic esophagitis. World J Gastroenterol 2009 Jan 7; 15 (1): 17-24
18. Abid S, Mumtaz K, Jafri W, et al. Pill-induced esophageal injury: endoscopic features and clinical outcomes. Endoscopy 2005 Aug; 37 (8): 740-4
19. Richter JE. The patient with refractory gastroesophageal reflux disease. Dis Esophagus 2006; 19 (6): 443-7
20. Keate RF, Williams JW, Connolly SM. Lichen planus esophagitis: report of three patients treated with oral tacrolimus or intraesophageal corticosteroid injections or both. Dis Esophagus 2003; 16 (1): 47-53
21. Hirschowitz BI, Simmons JL, Johnson LF, et al. Risk factors for esophagitis in extreme acid hypersecretors with and without Zollinger-Ellison syndrome. Clin Gastroenterol Hepatol 2004 Mar; 2 (3): 220-9
22. Furuta T, Shirai N, Sugimoto M, et al. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. Drug Metab Pharmacokinet 2005 Jun; 20 (3): 153-67
23. Turner BG, Saltzman JR, Hua L, et al. Endoscopic pH monitoring for patients with suspected or refractory gastroesophageal reflux disease. Can J Gastroenterol 2007 Nov; 21 (11): 737-41
24. Mainie I, Tutuian R, Shay S, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut 2006 Oct; 55 (10): 1398-402
25. Zerbib F, Roman S, Ropert A, et al. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. Am J Gastroenterol 2006 Sep; 101 (9): 1956-63
26. Fass R, Murthy U, Hayden CW, et al. Omeprazole 40 mg once a day is equally effective as lansoprazole 30 mg twice a day in symptom control of patients with gastro-oesophageal reflux disease (GERD) who are resistant to conventional-dose lansoprazole therapy: a prospective, randomized, multi-centre study. Aliment Pharmacol Ther 2000 Dec; 14 (12): 1595-603
27. Brillantino A, Monaco L, Schettino M, et al. Prevalence of pathological duodenogastric reflux and the relationship between duodenogastric and duodenogastrooesophageal reflux in chronic gastrooesophageal reflux disease. Eur J Gastroenterol Hepatol 2008 Dec; 20 (12): 1136-43
28. Hoffman I, Tertychnyy A, Ectors N, et al. Duodenogastro-esophageal reflux in children with refractory gastro-esophageal reflux disease. J Pediatr 2007 Sep; 151 (3): 307-11
29. Burke CA, Achkar E, Falk GW. Effect of pneumatic dilation on gastroesophageal reflux in achalasia. Dig Dis Sci 1997 May; 42 (5): 998-1002
30. Jacobson BC, Somers SC, Fuchs CS, et al. Body-mass index and symptoms of gastroesophageal reflux in women. N Engl J Med 2006 Jun 1; 354 (22): 2340-8
31. An evidence-based appraisal of reflux disease management: the Genval Workshop Report. Gut 1999; 44 Suppl. 2: S1-16
32. Fackler WK, Ours TM, Vaezi MF, et al. Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. Gastroenterology 2002 Mar; 122 (3): 625-32
33. Katz PO, Anderson C, Khoury R, et al. Gastro-oesophageal reflux associated with nocturnal gastric acid breakthrough on proton pump inhibitors. Aliment Pharmacol Ther 1998 Dec; 12 (12): 1231-4
34. Koek GH, Sifrim D, Lerut T, et al. Effect of the GABA(B) agonist baclofen in patients with symptoms and duodeno-gastro-oesophageal reflux refractory to proton pump inhibitors. Gut 2003 Oct; 52 (10): 1397-402
35. Connor F. Gastrointestinal complications of fundoplication. Curr Gastroenterol Rep 2005 Jun; 7 (3): 219-26
36. Peters JH, DeMeester TR, Crookes P, et al. The treatment of gastroesophageal reflux disease with laparoscopic Nissen fundoplication: prospective evaluation of 100 patients with "typical" symptoms. Ann Surg 1998; 228 (1): 40-50
37. DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastroesophageal reflux disease: evaluation of primary repair in 100 consecutive patients. Ann Surg 1986; 204 (1): 9-20
38. Bittner HB, Meyers WC, Brazer SR, et al. Laparoscopic Nissen fundoplication: operative results and short-term follow-up. Am J Surg 1994 Jan; 167 (1): 193-8; discussion 9-200
39. Collard JM, de Gheldere CA, De Kock M, et al. Laparoscopic antireflux surgery: what is real progress? Ann Surg 1994 Aug; 220 (2): 146-54
40. Walker SJ, Baxter ST, Morris AI, et al. Review article: controversy in the therapy of gastro-oesophageal reflux disease.

Long-term proton pump inhibition or laparoscopic anti-reflux surgery? Aliment Pharmacol Ther 1997 Apr; 11 (2): 249-60

41. Swoger J, Ponsky J, Hicks DM, et al. Surgical fundoplication in laryngopharyngeal reflux unresponsive to aggressive acid suppression: a controlled study. Clin Gastroenterol Hepatol 2006 Apr; 4 (4): 433-41
42. Mathew G, Watson DI, Myers JC, et al. Oesophageal motility before and after laparoscopic Nissen fundoplication. Br J Surg 1997 Oct; 84 (10): 1465-9
43. Jamieson GG, Watson DI, Britten-Jones R, et al. Laparoscopic Nissen fundoplication. Ann Surg 1994 Aug; 220 (2): 137-45
44. Vakil N, Shaw M, Kirby R. Clinical effectiveness of laparoscopic fundoplication in a U.S. community [comment]. Am J Med 2003; 114 (1): 1-5
45. Watson DI, Jamieson GG, Baigrie RJ, et al. Laparoscopic surgery for gastro-oesophageal reflux: beyond the learning curve. Br J Surg 1996 Sep; 83 (9): 1284-7
46. Triadafilopoulos G, Dibaise JK, Nostrant TT, et al. Radiofrequency energy delivery to the gastroesophageal junction for the treatment of GERD. Gastrointest Endosc 2001; 53 (4): 407-15
47. Filipi CJ, Lehman GA, Rothstein RI, et al. Transoral, flexible endoscopic suturing for treatment of GERD: a multicenter trial. Gastrointest Endosc 2001 Apr; 53 (4): 416-22
48. Deviere J, Costamagna G, Neuhaus H, et al. Nonresorbable copolymer implantation for gastroesophageal reflux disease: a randomized sham-controlled multicenter trial. Gastroenterology 2005 Mar; 128 (3): 532-40
49. Liu JJ, Carr-Locke DL, Lee LS, et al. Endoluminal gastroplication for treatment of patients with classic gastroesophageal reflux symptoms and borderline 24-h pH studies. Scand J Gastroenterol 2004 Jul; 39 (7): 615-20
50. Chen YK, Raijman I, Ben-Menachem T, et al. Long-term outcomes of endoluminal gastroplication: a U.S. multicenter trial. Gastrointest Endosc 2005 Jun; 61 (6): 659-67
51. Rothstein RI, Pohl H, Grove M, et al. Endoscopic gastric plication for the treatment of GERD: two year follow-up results [abstract]. Am J Gastroenterol 2001; 96 (9 Suppl.): S35

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