Current status of gastroesophageal reflux disease : diagnosis and treatment

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Abstract

Aims : **The aim of this study was to explore the recent advances in diagnosis and treatment of gastroesophageal reflux disease (GERD).**

Methods : **Previous studies were searched using the terms "gastroesophageal reflux disease" and "diagnosis" or "treatment" in Medline and Pubmed. Articles that were not published in the English language, manuscripts without an abstract, reviews, meta-analysis, and opinion articles were excluded from the review. After a preliminary screening, all of the articles were reviewed and synthesized to provide an overview of the contemporary approaches to GERD.**

Results : GERD has a variety of symptomatic manifestations, which can be group**ed into typical, atypical and extra-esophageal symptoms. Those with the highest specificity for GERD are acid regurgitation and heartburn. In the absence of other alarming symptoms, these symptoms allow one to make a presumptive diagnosis of GERD and initiate empiric therapy. GERD-associated complications include erosive esophagitis, peptic stricture, Barrett's esophagus, esophageal adenocarcinoma and pulmonary disease. Management of GERD may involve lifestyle modifications, medical and surgical therapy. Medical therapy involves acid suppression, which can be achieved with antacids, histamine-receptor antagonists or proton-pump inhibitors. Whereas most patients can be effectively managed with medical therapy, others may go on to require anti-reflux surgery after undergoing a proper pre-operative evaluation.**

Conclusion : **The management of this disease requires a complex approach. Maintenance therapy of GERD after using anti-secretory drugs should be continuously monitored.** (Acta gastroenterol. belg., **2017**, 80, **396-404**).

Key words : Gastroesophageal reflux disease ; Esophageal disease ; Acid suppression ; Surgical treatment; Medical therapy.

Introduction

The prevalence (from 11% to 24%) of gastroesophageal reflux disease (GERD) is high in the western world and is becoming a common and serious global problem (1). The high morbidity associated with GERD combined with the high medical costs has created a significant socioeconomic burden. GERD manifests as a wide range of symptoms that can be subdivided into typical, atypical and extraesophageal symptoms. Although GERD symptoms are mild and not life threatening, GERD has a great impact on the quality of life of patients (2). Patients with persistent reflux symptoms on acid suppression therapy have reduced physical and mental health (1,2). Furthermore, the reduction in mental health-related quality of life at baseline impairs symptomatic response to acid suppression therapy (2).

In addition, the increasing prevalence of gastro-esophageal reflux symptoms (GERS) is alarming because it is likely to contribute to an increasing incidence of adenocarcinoma of the esophagus in the western population (3,4). Recently, the prevalence of GERD has increased over time in all populations, not only in western countries (5). Therefore, it is important to understand GERD from both the basic science and the management perspectives. The purpose of this study was to explore the recent advances in diagnosis and treatment of GERD.

Methods

All papers published from January 1995 through December 2015 describing patients affected by GERD were obtained by searching MEDLINE (National Library of Medicine, Bethesda, Maryland, USA) and EMBASE using the keywords "gastroesophageal reflux disease (GERD)" and "diagnosis" or "treatment". Articles not published in the English language were excluded from the review. Figure 1 shows a summary of the article selection process.

The articles were reviewed, and only reports of original studies were retained. Manuscripts without an abstract (assumed not to be original), reviews, meta-analysis, and opinion articles, were excluded. After selecting the articles, relevant information was extracted and classified with respect to the basic science, the clinical indicators (symptomatology, visits to the emergency department, and hospitalization), and the information source (diagnosis, treatment, or therapy, or management).

The searches were performed in November and December 2015. Using the search terms described above, 2,491 documents were retrieved from Medline. After screening the articles, 101 were considered to be relevant.

Diagnosis

Management of patient with GERD requires a high quality of accurate diagnosis of GERD that prompted therapy (Fig. 2) (6-10).

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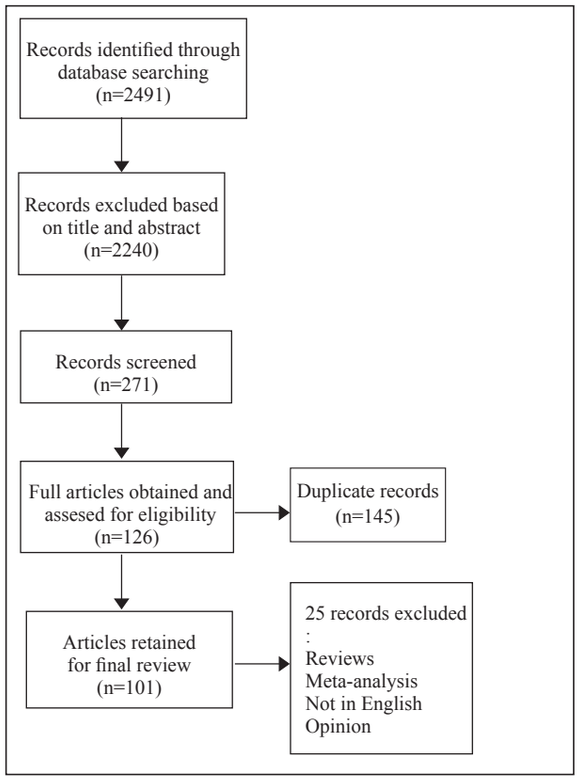

Figure 1. — Flow chart of article searching procedures.

Clinical picture

Typical symptoms include heartburn and acid regurgitation. Both symptoms have a high specificity but low sensitivity for GERD (11,12). Atypical manifestations include weight loss, gastrointestinal bleeding, nausea, and/or vomiting are also important for making a diagnosis of GERD(13,14). Atypical symptoms may be suggestive of GERD, but these symptoms may also overlap with other conditions such as peptic ulcer disease, achalasia, gastritis, dyspepsia and gastroparesis, which must be included in the differential diagnosis (Fig. 3) (11-14).

The absence of GERD in a patient with typical heartburn symptoms suggests a diagnosis of functional heartburn (12), which should be ruled out. This latter condition presents as burning retrosternal discomfort/ pain. The above-mentioned criteria should be fulfilled over the preceding 3 months, with the onset of symptoms of at least 6 months prior to diagnosis (15). In addition, there are various extraesophageal symptoms including chronic cough, asthma, laryngitis and dental erosions (16,17). However, extraesophageal symptoms are often secondary to a host of other conditions and should not uniformly be attributed to a diagnosis of GERD, especially when typical symptoms are absent.

Empirical therapy

The patients with a history suggestive of uncomplicated GERD with typical symptoms of heartburn and/or regurgitation can be offered empiric treatment. Typical symptoms that are responsive to acid suppression offer additional evidence for pathologic esophageal acid exposure, and it is reasonable to assume a diagnosis of GERD in patients who respond to appropriate therapy (11). However, if typical symptoms do not improve, further evaluation is warranted to confirm the existence of GERD or to search for an alternate diagnosis.

The previous study illustrated that a minority of patients, even when taking a high dose of a proton pump inhibitor (PPI), will continue to have objective evidence of pathologic esophageal acid exposure on ambulatory pH monitoring[18], although this is likely to be a result of medication non-compliance or PPI resistance.

Ambulatory pH monitoring

Ambulatory reflux monitoring allows for the direct measurement of reflux from the stomach to the esophagus and is typically used to evaluate patients with persistent symptoms despite medical therapy in order to confirm the diagnosis, particularly those without endoscopic evidence of GERD. It can also be employed to monitor the control of reflux in patients with persistent symptoms while on therapy (11). Lastly, ambulatory reflux monitoring is also recommended in patients with

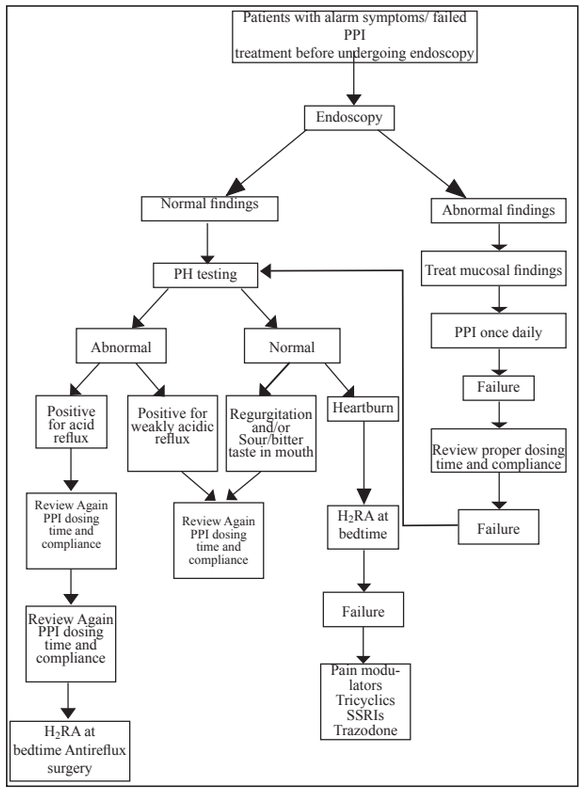

Figure 2. — Flowchart of diagnosis and management of gastroesophageal reflux disease 6-10.
Note : PPI, proton-pump inhibitor; H2RA, histamine-2-receptor antagonist; SSRI, selective serotonin re-up-take inhibitor; TLESR, transient lower esophageal sphincter relaxation.

negative endoscopy findings prior to undergoing anti-reflux surgery in order to confirm the diagnosis. Recently, a wireless capsule and a transnasal catheter monitoring device (pH alone or combined pH-impedance) have been developed (19). The wireless capsule decreases patient discomfort. The capsule (conventionally placed 6 cm above the squamocolumnar junction) measures the pH and transmits the data via a radiofrequency signal to a small receiver clipped onto the patient's belt (20). Compared to the traditional catheter-based systems, this approach allows the patient to resume normal activity without the conspicuous presence of a transnasal catheter and also allows for additional recording time (typically 48-hour compared to 24-hour recording with catheter-based monitoring). Another advantage of a wireless capsule is the fixed position of the capsule on the esophageal wall in comparison to catheter-based systems where migration with swallowing or talking has been shown to occur (21,22). Potential disadvantages include the additional expense due to endoscopic placement, early detachment in a minority of patients, patient discomfort that could require removal via repeat endoscopy, as well as over-diagnosis of GERD due to ingestion of acidic foods (23,24). Transnasal catheter pH testing is limited by patient tolerance and the limitation of 24-hour monitoring restriction, but it has the unique advantage of adding impedance that allows a distinction to be made between acid and non-acid gastroesophageal reflux. Impedance monitoring detects changes in the resistance to electrical current across adjacent electrodes so that the antegrade and retrograde bolus transit of both liquids and gas can be differentiated. Due to the ability to detect both acid as well as nonacid reflux, impedance-pH monitoring has greater sensitivity than pH monitoring alone in the detection of gastroesophageal reflux (25). Both wireless capsule and catheter-based systems can be used for evaluation of GERD in patients not taking acid suppression (26).

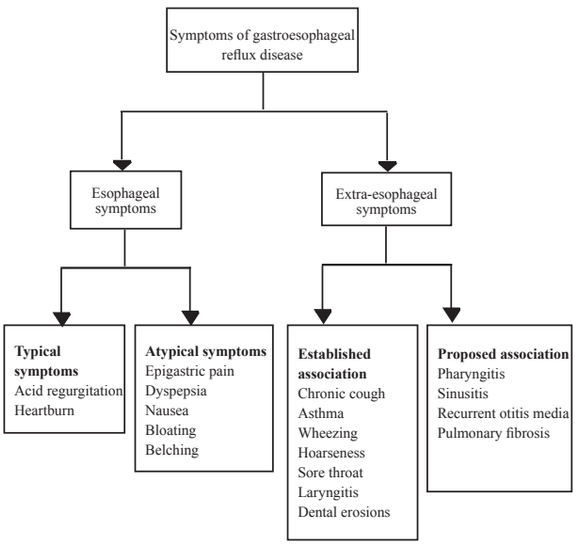

Figure 3. — Summary the symptoms of gastroesophageal reflux disease11-14.

Upper endoscopy

Upper endoscopy can be used to evaluate the effect of GERD on the esophageal mucosa and to obtain biopsies of concerning lesions (*e.g.,* Barrett's metaplasia, strictures or masses). However, there are limitations to upper endoscopy in the diagnosis of GERD. While an endoscopic examination showing esophagitis or Barrett's esophagus essentially confirms the diagnosis of GERD, a normal endoscopy does not necessarily rule it out. In fact, approximately 40% of patients with typical signs and symptoms of GERD will have normal endoscopic findings (27). Therefore, an upper endoscopy is not required for the diagnosis, especially in young adults. Indications for performing endoscopy include the following (27,28) : 1) if symptoms of GERD persist or relapse after PPI treatment, 2) evaluation of GERD-associated complications and alternative diagnoses as well as placement of wireless capsule pH probes, 3) patients at risk for esophageal adenocarcinoma. The combination of moderate to severe typical symptoms and endoscopic changes are highly specific (97%) for GERD (29).

Barium esophagram

Barium esophagram does not give accurate data in the evaluation of GERD. Barium radiography is no longer recommended for the diagnosis of GERD due to its low sensitivity and specificity (30). However, because the testing of esophageal motility reveals the location of the lower esophageal sphincter pressure and esophageal peristalsis in GERD patients, barium radiography facilitates the accurate placement of reflux monitoring probes. In conjunction with endoscopic evaluation, barium radiography is also frequently used to evaluate GERD-related complications (*e.g.,* peptic stricture) as well as dysphagia in the post anti-reflux surgery patient (11,19). The barium esophagram is an important part of the assessment and management of patients with GERD before and after antireflux procedures (31). The barium esophagram is better at demonstrating the anatomic landmarks after antireflux surgery than the findings on the other examination, e.g. edoscopy (31,32).

Esophageal manometry

Esophageal manometry is most useful for evaluating patients with suspected esophageal GERD who have not responded to PPI therapy and have normal findings on endoscopy. Although disruption of the anti-reflux barrier (gastroesophageal junction) and dysfunction of esophageal peristalsis are common in GERD patients, these findings are not diagnostic and, therefore, there is no manometric pattern that is pathognomonic for reflux

(33). The role of manometry in the evaluation of GERD remains limited to localizing the lower esophageal sphincter for potential pH monitoring and preoperative testing for the identification of significant motor disorders such as achalasia or scleroderma. Evolving technology suggests that high-resolution manometry has superior sensitivity to conventional manometry in recognizing atypical cases of achalasia and distal esophageal spasms (33). The esophageal manometry is valued in refractory GERD to exclude motility disorder. Otherwise, this test is not recommended for the diagnosis of GERD.

Real-time Magnetic Resonance Imaging

A small angle (His angle) between the esophagus and the fundus of the stomach acts as a flap valve and anti-reflux barrier. A wide angle results in a dysfunction of the esophagogastric junction leading to GERD. Real-time magnetic resonance imaging (MRI) at 50 ms resolution (20 frames per second) has been used for the diagnosis of GERD (34). In a study, twenty-two volunteers and 22 patients with GERD were enrolled to assess the transport of pineapple juice through the esophagogastric junction and to test for reflux during Valsalva (34,35). It was found that the intra-abdominal part of the esophagus was bent toward the left side, resulting in an angle of 75.3 ± 27.4, which was significantly larger during Valsalva. Reflux and several pathologies were detected in 50% of study patients. This study suggested that non-invasive real-time MRI could potentially be used to diagnosis the existence of pathological changes that may lead to GERD. The limitations of MRI are high cost, not widely available, and more studies required.

Table 1. — **Treatment of gastroesophageal reflux disease**

			Methods	
	Life modifications		Medical therapies	Surgical therapies
1.	Weight loss	1.	Anti-refluxants and anti-acids	1.Fundoplication
2.	Head of bed elevation	2.	Acid suppression	Nissen fundoplication
3.	Avoidance of nighttime meals		H2RAs PPIs	Hill fundoplication Belsey fundoplication
4.	Elimination of trigger foods (e.g. chocolate, caffeine and alcohol)	3. 4.	Prokinetic drugs Mosaprides GABA	Dor fundoplication Toupet fundoplication Robotic-assisted esophageal surgery
5.	Avoid recumbency 3 hours postpran-dially		Baclofen	2. Sphincter augmentation Magnetic sphincter augmentation

Note: H2RAs : histamine-2-receptor antagonists ; PPIs : proton-pump inhibitors ; GABA : gama-aminobutyric acid.

Treatment

Lifestyle modifications

(Table 1) Lifestyle interventions are important in GERD patients (36,37). Numerous studies have indicated that lifestyle and diet modifications decrease the distal esophageal acid exposure and/or GERD symptoms. These lifestyle changes include weight loss, elevation of the head of the bed, avoidance of nighttime meals, and elimination of trigger foods such as chocolate, caffeine and alcohol (38-41). One study suggested a positive association between increasing BMI (42). Interestingly, BMI was found to be associated with symptoms of GERD in both normal weight and overweight women, and even moderate weight gain among individuals of normal weight was found to cause or exacerbate symptoms (42). Therefore, weight loss is recommended for GERD patients who are overweight or who have had recent weight gain. For nighttime reflux symptoms, patients should elevate the head of the bed and avoid recumbency 3 hours after eating. Recurrence was diagnosed when patients complained of GERD symptoms requiring additional medication after an initial recovery with 4-8 weeks of PPI treatment. A shorter dinner-to-bedtime interval was the most significant factor influencing the recurrence of GERD, and patients who usually slept within 3-hour after eating had higher recurrence rates (43). It has been found that regular dietary intake, noodles, spicy food, fatty meals, sweets, alcohol, breads, carbonated drink and caffeinated drink are associated with symptom aggravation in GERD (44). Despite strict compliance, lifestyle changes alone are frequently inadequate for controlling symptoms and medical therapy often becomes necessary.

Thus, weight-loss for overweight or obese patients and elevating the head of the bed when recumbent for individuals with heartburn or regurgitation are important recommendations for patients with GERD.

Medical therapy

Anti-refluxants and Anti-acids

Alginate-based formulations have been available for the past 30 years. Alginate forms a gel following precipitation in the presence of gastric acid. The gel then traps carbon dioxide, creating a substance that floats on the surface of the gastric contents similar to a raft on water (45-48). Alginate-based formulations are rapid and effective treatment for mild to moderate GERD (49,50). Antacids are also effective in achieving relief from heartburn (45,46).

Acid Suppression

The mainstay of treatment of GERD is acid suppression. In the past few decades, this field has undergone rapid evolution. Several classes of

medications including antacids, histamine-2-receptor antagonists (H2RAs), and proton-pump inhibitors (PPIs) have been used for the treatment of GERD. H2RAs were first introduced in the 1980s and represented a specific pharmacological approach to controlling acid secretion (51). H2 antagonists, also called H2 blockers, are a class of medications that block the action of histamine at the histamine H2 receptors of the parietal cells in the stomach and can have their acid-inhibitory effect antagonized by histamine stimulation or cholinergic drive (51). H2RAs are relatively effective in treating symptoms of heartburn and have a rapid onset of action. Patients whose heartburn persists after 6 weeks of treatment with H2RAs are unlikely to respond to a prolonged course of treatment or to increased dosage (52,53).

The PPI (omeprazole) was first developed in 1989 and was followed by three additional agents with similar efficacies (lansoprazole, pantoprazole, and rabeprazole). Proton-pump inhibitors (PPIs) are a group of drugs whose main action is a pronounced and long-lasting reduction of gastric acid production. They are the most potent inhibitors of acid secretion available. PPIs act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H^+/K^+ ATPase, or, more commonly, the gastric proton pump) of the gastric parietal cells (54). PPIs have a half-life in human blood plasma of only 60-90 minutes, but because they covalently bind to the pump, the half-life of their inhibition of gastric acid secretion lasts an estimated 24 hours (54). For maximum serum concentration and efficacy, the best time to take the medication is when the largest numbers of proton pumps are active. Because meals stimulate proton pumps, a dose taken 15-60 minutes prior to a meal has the greatest effect on acid suppression (55). Therefore, the recommendation is for patients on once-daily PPIs take a dose before breakfast. Once-daily PPI therapy suppresses gastric acid for 11.2 to 15.3 hours during a 24-hour day (56).

When compared with H2RAs, PPIs lead to more complete healing of erosive esophagitis and better relief from heartburn and act nearly twice as fast (57). Additionally, erosive esophageal reflux disease (ERD) is more difficult to treat with H2RA compared with PPIs (58), and patients with ERD tend to have improved symptomatic relief with PPIs compared with patients with non-erosive esophageal reflux disease (NERD) (59). Therefore, maintenance PPI therapy at the lowest effective dose is recommended to treat erosive reflux disease as most patients will relapse after discontinuation of therapy (60). In general, PPIs are thought to be equally effective, and patients should be instructed to take these medications 30-60 min prior to meals, with the exception of dexlansoprazole, which can be taken irrespective of food intake. In contrast, patients with NERD can potentially be managed successfully with on-demand PPI or, alternatively, with less costly therapy such as H2RAs. The feasibility of step-down therapy in patients with GERD rendered asymptomatic with PPIs was evaluated in one study that reported 58% of patients in the step-down group were asymptomatic on either non-PPI therapy or no therapy at all after a 1-year follow-up. Of the patients who remained off PPIs, 59% required H2RAs (61). Given the high cost associated with indefinite PPI use, attempts should be made to treat patients with the least expensive yet effective medication, particularly in patients with NERD who may be able to control their symptoms with a maintenance dose of H2RAs. If symptoms recur, then maintenance PPI therapy should be reconsidered.

Patients with PPI-refractory GERD can be challenging to treat and are frequently referred to a gastroenterologist. First, compliance with medical therapy and proper dosing should be addressed. A study involving 10,159 patients with Barrett's esophagus and 48,965 GERD patients without Barrett's esophagus (BE) found that compliance of PPI prescriptions were only 66.6% and 60.4% of patients with BE and GERD, respectively (62). Given such high rates of noncompliance, it is important to obtain an accurate history to avoid unnecessarily escalating therapy. If symptoms are truly refractory to proper medical therapy, the dosing can be increased or an alternate PPI can be used. Both methods may lead to symptomatic improvement and both appear to be equally effective (63). If a patient has predominantly nighttime symptoms, more effective nocturnal acid suppression may be achieved with twice daily or nighttime dosing (64). Another approach in the PPI-refractory patient involves the addition of nighttime H2RAs to twice daily PPI therapy for persistent nighttime symptoms. Though a contested issue, the benefit from this approach is likely to be temporary as studies have shown that after one month of uninterrupted H2RA therapy, gastric acidity returns to pre-H2RA levels (65).

Prokinetic (motility) therapy and Other therapies

A gastroprokinetic agent acts as a selective 5-hydroxytryptamine 4 (5HT4) agonist that increases acetylcholine release from parasympathetic nerve endings and promotes bowel motility as well as gastric emptying (66). Yamaji *et al* (67) conducted a randomized study to compare the patients treated with omeprazole plus mosapride (5HT4 agonist) (30 patients) to patients treated with omeprazole plus placebo (30 patients). The authors found that the addition of mosapride to omeprazole was no more effective at controlling reflux symptoms than omeprazole alone in patients with NERD (65). According to the previous studies (67,68), prokinetic therapy did not lead to additional amelioration of reflux symptoms in the treatment of GERD. A formulation of omeprazole combined with an anti-acid and alginate may have some advantages over the parent compound including being taken without meals and perhaps a more rapid onset of action (69,70).

Baclofen, also known as β-(4-chlorophenyl)-γ-aminobutyric acid (β-(4-chlorophenyl)-GABA), is a central nervous system depressant used as a skeletal

muscle relaxant and is primarily used to treat spasticity. It is also used in topical pain creams as a muscle relaxant (71). A study showed that baclofen administered at bedtime reduces postprandial reflux events, decreases sleep-related reflux events and markedly improves objective and subjective sleep parameters compared with placebo. Baclofen has also been shown to reduce acid exposure in normal individuals and in patients with GERD by inhibiting transient lower esophageal sphincter relaxations, which are thought to be the primary cause of reflux events (72). Unfortunately, its side effects often preclude continued use of this medication and include drowsiness (up to 63%), dizziness (5%-15%), weakness (5%-15%), and fatigue (2%-4%) (67).

Tricyclic antidepressants (TCAs) could be effective in the treatment of symptoms related to a hypersensitive esophagus (73), more effectively than does placebo. TCA use may decrease the tone of the lower esophageal sphincter, salivation, or oesophageal motility and thus exacerbate reflux symptoms (74).

Long-term (maintenance) therapy

Many patients with GERD require long-term therapy. The major goal of maintenance therapy is to keep symptoms comfortably under control and to prevent complications (75-77). For up to 20% of patients, only anti-acids and lifestyle modifications are required to reach this aim (76). Patients who have required PPIs for symptomatic relief often will have relapses and persistent esophagitis on the standard dose or even when taking higher doses of H2RA and/or are on prokinetic therapy (78,79). A full dose of H2RA given once daily, although effective for peptic ulcer disease, is not appropriate for GERD. Lower doses of PPI for maintenance do not guarantee to offer a safety advantage, although some PPIs (e.g. esomeprazole 20 mg and lansoprazole 15 mg) are recommended for lower maintenance doses. Essentially, only a fraction of the patients should remain on the highest dose (80). Indeed, it has been shown that maximum doses of PPIs are associated with longer durations between symptomatic relapses in patients with esophageal strictures requiring dilation (81,82).

Because many patients are treated with PPIs on a long-term basis, safety is a major concern. Retrospective studies have reported an increased incidence of a number of complications in patients taking PPIs (particularly higher than the recommended doses) such as community-acquired pneumonia (83), clostridium difficile infection (84), and hip fractures (85).

Surgical therapy

The majority of GERD patients will have mucosal disease and the majority of symptoms can be controlled with medical therapy. However, a small subset of patients exhibits symptoms that are, or appear to be, refractory to medical therapy, patients with complications of reflux such as stricture, Barrett's esophagus, persistent reflux symptoms despite acid suppression, asthma, or patients who are intolerant to medication, poor compliance with medication, or who are medication dependent and unwilling to take long-term medication. In these cases, surgical therapy is the other treatment option (86).

How to choose the operation? Rudolf Nissen described the first fundoplication in the 1950s for treatment of severe reflux esophagitis (86). His original procedure used a 360 degree wrap of the fundus of the stomach around the esophagus by plication of both the anterior and posterior walls of the gastric fundus around the lesser curvature. Although the standard Nissen fundoplication has been modified many times, laparoscopic Nissen fundoplication is now considered the standard surgical approach for treatment of GERD. Compared to laparotomy antireflux surgery, the short- and medium-term outcomes of laparoscopic anti-reflux surgery are quite good at improving the typical symptoms of GERD ; however, in the long-term, positive results may diminish (86). It was found that the complication rate for patients treated with laparoscopic antireflux surgery was lower than that of the patients treated with open (laparotomy) antireflux surgery (87). For the patient with normal length but decreased motility, a complete fundoplication is discouraged; however, the laparoscopic or open Toupet or Hill or transthoracic Belsey procedure could be applied. Robotic-assisted esophageal surgery (88), a newer minimally-invasive technique, offers a safe and effective method of treating GERD, but more studies including randomized controlled trials are needed.

A new surgical option became available when the US Food and Drug Administration (FDA) approved the LINX device for implantation (89). This is a magnetic sphincter augmentation system designed to support the lower esophageal sphincter in much the same way as a fundoplication. Unlike a fundoplication, the device is dynamic, being made up of multiple interlinked titanium-coated rare-earth magnets. Results from clinical trials have been very promising, with excellent results relative to control of reflux and with fewer adverse effects (e.g., dysphagia, gas-bloat) that may accompany a traditional fundoplication. Additionally, the safety profile seems to be very good. However, there is no one best operation for all patients, more studies evaluating the surgical treatments of GERD are needed in the future.

Comparing surgical with medical therapy for chronic GERD

GERD is a chronic, relapsing disease. A long-term management plan is required for each individual patient. Maintenance treatment with PPI therapy may be an option, offering high rates of symptom resolution and healing of esophagitis (90). However, some patients are reluctant to take long-term medication and may prefer to have anti-reflux surgery. A number of controlled studies have been undertaken comparing open anti-reflux surgery and laparoscopic antireflux surgery (LARS) (99)

or open anti-reflux surgery and medical therapy (91-93). The LOTUS (Long-Term Usage of Esomeprazole vs. Surgery for Treatment of Chronic GERD) trial compared maintenance therapy by esomeprazole (dose-adjusted when required) with standardized LARS in patients who responded well to acid-suppressive therapy (90). This multicenter clinical trial showed that estimated remission rate at 5 year were 92% (95% CI 89%-96%) in the esomeprozole group and 85% (95% CI 81%-90%) in the LARS group (log-rank P = 0.048). The difference was no longer statistically significant following best-cases scenario modeling of effects of study drop-out. In other words, either treated by drug-induced and suppression with esomeprozole of by LARS, most patients achieve and remain in remission at 5 years (90). In summary, both medical therapy and LARS are similar effective and well-tolerated for control GERD (90,94). However, proper patient selection and experienced physician are critical to achieve excellent outcomes.

Diagnosis and management of refractory symptoms

PPI-refractory reflux symptoms is defined as symptoms (heartburn and/or regurgitation) which are not responding to a stable double dose of a PPI during a treatment period of at least 12 weeks and patients continuing to report troublesome symptoms while on PPI at least 3 times a week for the last 3 months (9). The symptom burden must be to a degree that impairs quality of life, and symptoms must be reflux-related. Approximately 10% to 40% of patients with GERD are resistant or partial responders to PPI (95,96). Many of these patients do not have GERD, but suffer from functional heartburn of dyspepsia. The potential mechanism underlying failure of PPI treatment in patients with reflux-related symptoms include persistence of isolated mixed acid, weakly acidic, bile, or gas reflux, impaired esophageal mucosal integrity, chemical or mechanical hypersensitivity to refluxates and psychological comorbidity (97-99). Patients with persistent reflux symptoms despite a 2-month double dose PPI therapy should be further investigated. If symptoms are clearly related to persistent reflux, baclofen, anti-reflux surgery can be considered (9). Failure of PPIs is one of the most common indications for antireflux surgery (100,101). Anti-reflux surgery can be a valuable option in patients with typical reflux symptoms with inadequate response to PPIs.

Conclusions

GERD is a common disease and has become a socioeconomic burden worldwide. GERD is multi-factorial, and the management of this disease requires a complex approach in the diagnostic workup and in choosing appropriate and effective medical and surgical treatment (Fig. 2). It is therefore important to recognize, diagnose and properly treat patients with GERD in order to avoid detrimental effects on the quality of life and the development of GERD-related complications (e.g., erosive esophagitis, Barrett's esophagus).

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Author contributions

Chuang TW contributed to the study design, data collection, analysis, and drafting; Chen SC contributed to the study design, data collection, and drafting; Chen KT was the leading investigator and contributed to the conception, study design, drafting, and revision; all authors approved the final version of the manuscript.

Conflict-of-interest statement

Authors declared no conflict of interests for this article.

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