

DIAGNOSIS AND TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

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Abstract

Gastroesophageal reflux is defined as a common physiologic phenomenon encountered intermittently by a large population, especially following a feed. Gastroesophageal reflux disease (GERD) happens if the number of gastric juices that refluxes into the esophagus passes the accepted limit, making symptoms with or without correlated esophageal mucosal injury (i.e., esophagitis). Diagnosis and treatment guidelines of gastroesophageal reflux disease (GERD) were announced in 1995 and updated in 2005 and lastly reviewed in 2013 by the American College of Gastroenterology (ACG). These and other guidelines undergo periodic review. Advances continue to be made in GERD, leading us to review and revise previous guideline statements. Here we aimed to review the different updated guidelines of diagnosis and treatment of Gastroesophageal reflux disease (GERD). A web-based search utilizing the advanced characteristics of different databases like PubMed, Google Scholar, Embase, Scopus, and Cochrane electronic databases was carried out.

Keywords: Gastroesophageal reflux disease (GERD), Updates, Guidelines, Diagnosis, and Treatment.

Introduction

Gastroesophageal reflux disease (GERD) is increasingly common resulting in a growing economic burden on health service budgets, especially in western countries. Proton pump inhibitors are effective in healing erosive changes and in relieving reflux symptoms, but there is still much debate on how to measure symptom improvement and what constitutes symptom resolution. In clinical studies of erosive esophagitis, treatment outcome has traditionally been based on endoscopy (and sometimes on pH-metry). From the patient's point of view, however, the important consideration is relief of their symptoms, not only heartburn but all symptoms, both typical and atypical. This consideration is particularly important in non-erosive reflux for there are no endoscopic changes to assess; relief of symptoms is therefore the only measure.

The assessment of symptoms by scales and questionnaires is widely used for diagnosis, epidemiology, and for assessing treatment response in GERD studies. Almost all

reports of GERD therapy include data on symptom relief, but a literature search shows wide variation how such changes are reported. In addition, some scales are unsuitable for assessing response to treatment as they were developed mainly for diagnosis, or concentrated only on some symptoms, or had not undergone full formal psychometric validation.

Psychometric validation is essential for instruments used to assess surrogate markers (for example, symptoms or quality of life, QoL), particularly when they are designed to be used as the primary outcome measure in clinical trials. Two statements from the current International Conference on Harmonization (ICH) guidelines make the points: (a) 'when a rating scale is used as a primary variable, it is especially important to address factors such as content validity, inter- and intra-rater reliability and responsiveness for detecting changes in the severity of the disease' (CPMP/ICH/363/96 2.2.3), and (b) 'If a trial ... lacks assay sensitivity, it will fail to lead to a conclusion of efficacy. In contrast ..., the trial may find an ineffective treatment to be non-inferior and

could lead to erroneous conclusion of efficacy' (CPMP/ICH/364/96 1.5).

Hence, there is a need to develop an instrument that accurately evaluates typical and atypical GERD symptoms, and can be used to assess treatment response during and after therapeutic interventions in GERD patients. This new scale should be appropriate for both erosive and non-erosive GERD and, when assessing the response to treatment, highly sensitive to changes in symptoms. It should also encompass the whole spectrum of GERD symptoms, and contain comprehensive information about their intensity and frequency. Finally, the scale should be suitable for self-assessment by the patient, practical to use, easy to understand, responsive to rapid changes, and internationally validated. (1)

Materials and Methods:

A web-based search utilizing the advanced characteristics of different databases like PubMed, Google Scholar, Embase, Scopus, and Cochrane electronic databases was carried out. The MeSH and other keywords like; Gastroesophageal reflux guidelines, treatment protocols of GERD, recent trends of GERD diagnosis and etc., were used to search the databases. The search included the latest studies published from 1995 to 2020, and the search was limited to studies published in English.

Diagnosis:

Evidence-based limitations exist when trying to assess the validity of the diagnostic modalities for GERD. Most studies have flawed methods because no gold standard exists. However, the calculated numbers are helpful in providing a framework to assess available options. Recent studies suggest that combining diagnostic modalities (omeprazole challenge test [daily omeprazole for two weeks], 24-hour pH monitoring, and endoscopy) may increase the sensitivity for diagnosis of GERD (approaching 100%), but this approach is not practical in the routine clinical setting. 24-hour pH monitoring offers adequate sensitivity and specificity in establishing a diagnosis of GERD in cases that do not readily respond to anti-secretory therapy. It can also help with patient compliance by establishing that acid production has been eliminated or reduced to zero. The UMHS approach to 24-hour pH monitoring includes: scheduling, availability, report turnaround time, patient satisfaction, cost, and insurance coverage. (2)

Symptoms of GERD:

Common signs and symptoms of GERD include:

- A burning sensation in your chest (heartburn), usually after eating, which might be worse at night
- Chest pain
- Difficulty swallowing
- Regurgitation of food or sour liquid
- Sensation of a lump in your throat

If you have nighttime acid reflux, you might also experience:

- Chronic cough
- Laryngitis
- New or worsening asthma
- Disrupted sleep (3)

History

Since GERD occurs with few if any abnormal physical findings, a well-taken history is essential in establishing the diagnosis of GERD. Symptoms of classic burning in the chest, with sour or bitter taste, and acid regurgitation have been shown to correctly identify GERD with a sensitivity of 89% and specificity of 94%. Up to 1/3 of patients with GERD will not report the classic symptoms of heartburn and regurgitation. However, symptom frequency, duration and severity are equally distributed among patients with varying grades of esophagitis and Barrett's esophagus and cannot be used reliably to diagnose complications of GERD. There may also be some symptom overlap with other conditions (non-cardiac chest pain, cough, etc.). (4)

PPI diagnostic test. A favorable symptomatic response to a short course of a PPI (once daily for two weeks) is considered to support a diagnosis of GERD when symptoms of noncardiac chest pain are present. A meta-analysis found that a successful short-term trial of PPI therapy did not confidently establish a diagnosis of GERD (sensitivity 78%, specificity 54%) when 24-hour pH monitoring was used as the reference standard. This may be due to an observed clinical benefit of PPIs in treating other acid-related conditions (as seen in the heterogeneous dyspeptic population), patients with enhanced esophageal sensitivity to acid (without true GERD), or even due to a placebo effect. In those with non-cardiac chest pain, an empiric trial of high-dose omeprazole (40 mg AM, 20 mg PM) had a sensitivity of 78% and specificity of 85%. Standard dosages may have lower sensitivity and specificity. (5)

Empiric or therapeutic trial. Diagnostic modalities cannot reliably exclude GERD even if they are negative. Therefore, an empiric trial of anti-secretory therapy may be the most expeditious way in which to diagnose GERD in those with classic symptoms and who do not have symptoms suggestive of complications (eg, carcinoma, stricture). (See discussion of "step-up" therapy and "step-down" therapy in treatment section.) (6)

Empiric therapy should be tried for two weeks for patients with typical GERD symptoms. Treatment can be initiated with standard dosage of either an H2RA twice daily (on demand, taken when symptoms occur) or a PPI (30-60 minutes prior to first meal of the day), with drug selection depending on clinical presentation and appropriate cost-effectiveness and the end point of complete symptom relief. (See Figure 1 and costs in Table 4). If symptom relief is not adequate and H2RA twice daily was initially used, then PPI daily should be used. If PPI daily was initially used, then

increase to maximum dose PPI daily or twice daily (30-60 minutes prior to first and last meals). (7)

For patients who initially present with more severe and more frequent symptoms of typical GERD, treatment may be initiated with higher and more frequent dosages of an H2RA or PPI. If symptom relief is not adequate from the initial dose, then increase potency or frequency as needed to obtain complete symptom relief: high-dose H2RA to PPI daily, PPI daily or maximum dose PPI daily or twice daily. If there is no response when using maximal doses and frequencies, then diagnostic testing should be performed after 8 weeks of therapy. (8)

If the patient responds with symptom relief, give 8-12 weeks of therapy, ie, enough to heal undiagnosed esophagitis. If the patient has complete symptom relief at 8-12 weeks, taper over 1 month to lowest effective dose of the medication that gives complete relief, eg, H2RA on demand, PPI every other day. If symptoms recur, put patient back on the lowest effective medication and dose, and consider further testing depending on clinical presentation and course. (9)

Patients who present with atypical or extraesophageal manifestations take a longer time to respond to empiric therapy, and often require twice-daily dosing. If there is no improvement at all in symptoms after two months, further testing should be pursued. (10)

Laboratory diagnosis:

- Upper endoscopy. Your doctor inserts a thin, flexible tube equipped with a light and camera (endoscope) down your throat, to examine the inside of your esophagus and stomach. Test results can often be normal when reflux is present, but an endoscopy may detect inflammation of the esophagus (esophagitis) or other complications. An endoscopy can also be used to collect a sample of tissue (biopsy) to be tested for complications such as Barrett's esophagus.
- Ambulatory acid (pH) probe test. A monitor is placed in your esophagus to identify when, and for how long, stomach acid regurgitates there. The monitor connects to a small computer that you wear around your waist or with a strap over your shoulder. The monitor might be a thin, flexible tube (catheter) that's threaded through your nose into your esophagus, or a clip that's placed in your esophagus during an endoscopy and that gets passed into your stool after about two days.
- Esophageal manometry. This test measures the rhythmic muscle contractions in your esophagus when you swallow. Esophageal manometry also measures the coordination and force exerted by the muscles of your esophagus.
- X-ray of your upper digestive system. X-rays are taken after you drink a chalky liquid that coats and fills the inside lining of your digestive tract. The coating allows your doctor to see a silhouette of your esophagus, stomach and upper intestine. You may also be asked to swallow a barium

pill that can help diagnose a narrowing of the esophagus that may interfere with swallowing. (11)

- Esophageal pH and impedance monitoring and Bravo wireless esophageal pH monitoring: These tests both measure the pH levels in your esophagus. Your provider inserts a thin tube through your nose or mouth into your stomach. Then you are sent home with a monitor that measures and records your pH as you go about your normal eating and sleeping. You'll wear the esophageal pH and impedance monitor for 24 hours while the Bravo system is worn for 48 hours.

- Upper GI series: X-rays of your upper GI tract show any problems related to GERD. You drink barium, a liquid that moves through your tract as the X-ray tech takes pictures. (12)

Other Testing for GERD. Esophageal acid perfusion testing (also called Bernstein testing), esophageal sensory testing, and barium esophagram are not indicated for the diagnosis of GERD. Barium esophagram may be helpful in the preoperative phase of anti-reflux surgery or in the evaluation of major motor disorders (eg, achalasia, diffuse esophageal spasm) after a normal endoscopy

Management:

First: life style change:

There is a general view that various foods cause the GERD symptoms or increase these symptoms. In daily clinical practice, suspected foods are often restricted. The presence of GERD symptoms frequently in the postprandial period suggests that diet is an important factor for development of these symptoms. However, in the literature, there are conflicting results about which foods increase reflux. (13)

Although Nebel et al. have demonstrated that fried foods, spicy foods, and alcohol are the foods that most precipitate heartburn, the lack of a control group in this study, and that the amount of consumption of these food products is not specified, raises question marks. (14) No significant results could be obtained in the epidemiological large-population study in which Ruhl et al. investigated the relationship between erosive esophagitis and fat-rich diets. However, in the study conducted by Shapiro et al., reflux episodes were observed more frequently in patients eating fat-rich foods. Similarly, in the large-scale case-control study of El-Serag et al., the relationship between the total fat amount consumed daily and both non-erosive reflux disease and erosive esophagitis was documented. Shapiro et al. showed that cholesterol and saturated fatty acid rich diets and a high ratio of daily calorie consumption increased the risk of episodes (15)

In the large-population epidemiological study of Zheng et al. , no relationship could be detected between reflux and the consumption of vegetables, fruits, fish, meat, rice, bakery products, milk, sandwiches, potato, and fried or grilled food. (16)

In the case-control study conducted by Nilsson *et al.* with more than 40,000 people regarding the use of alcohol, no relationship could be detected between alcohol intake and reflux symptoms. In another large population case-control study, El-Serag *et al.* could find no relationship between the total amount of alcohol consumed daily and erosive or non-erosive GERD development. In the study in which they investigated the reflux inducing effects of various foodstuffs, Shapiro *et al.* showed that alcohol use did not increase the risk of reflux episodes. (17)

The relationship between salt intake and the development of reflux symptoms has also been documented in various publications. In large-scale population-based studies, consumption of salted fish or meat twice a week has been shown to be a risk factor for the development of reflux symptoms (OR: 1.3, CI: 1.1-1.5). The same study has also documented that adding extra salt to food increases the risk of reflux symptoms development

There is evidence suggesting that a fiber-rich diet is an important protective factor from reflux development. In the population-based study of Nilsson *et al.*, a decrease was observed in the development of reflux in patients consuming fiber more than 4%, and this risk was observed to further decrease as the amount of fiber consumption increased. Furthermore, it is concluded that increasing the intake of fiber in a diet reduces the risk of esophageal adenocarcinoma associated with reflux. (18)

There is an old study reporting that chocolate reduces the basal pressure of lower esophageal sphincter. In the 1988 dated study of Murphy and Castell, increased esophageal acid reflux was confirmed through esophageal pH monitoring after chocolate consumption. In the result of our systematic review of the literature, no clinical study investigating the relationship between chocolate and reflux was found other than this study. There are a limited number of data suggesting that fizzy drinks can also lead to reflux symptoms in addition to chocolate. Fass *et al.* observed in their multivariate analysis that the consumption of carbonated soft drinks increased nocturnal reflux symptoms. (19)

POSTURE

There is a variety of data suggesting that lying positions may affect the development of GERD symptoms. The effect of gravity on the clearance of acidic and non-acidic stomach contents, and the proceeding of reflux fluid in the esophagus towards more proximal locations (remaining longer while lying in the supine position) are responsible for acid reflux being more damaging at night. (18) Moreover, lying on the right side has been shown in various publications to enhance the effect of reflux. Though the mechanism has not been fully explained yet, increased temporary relaxations of the lower esophageal sphincter in the right lateral position are indicated to be responsible for this situation. Lying in the left lateral position is known to

locate the gastroesophageal junction above the level of stomach acid. (20)

In the study of Khoury *et al.* in which they investigated the relationship between the spontaneous sleeping position and nocturnal reflux episodes, reflux incidence was determined lower in those sleeping prone and in the left lateral position than those sleeping in the right lateral and supine positions. (21)

Smoking:

Although there are publications suggesting that smoking has an aggravating role in GERD pathogenesis, the mechanism of this effect has not yet been clarified. It has been shown in various studies that an abrupt decrease occurs in lower esophageal sphincter pressure during smoking. In these studies, it was found that the lower esophageal sphincter pressure completely returned to normal 5-8 minutes after smoking ceases

SECOND: pharmacological treatment:

1. Therapy Focused on Antacids and Alginate:

Antacid

Before H2RA development, antacids were widely used as initial treatment for patient with reflux symptoms. (22) Antacids are compounds containing different combinations, such as calcium carbonate, sodium bicarbonate, aluminum, and magnesium hydroxide. They provide rapid but short-term symptom relief by buffering gastric acid. Antacids are a convenient over-the-counter treatment for GERD, but only one-quarter of patients have symptom relief after antacid use. Nevertheless, these drugs have no efficacy in healing erosive esophagitis (23)

Alginate:

Alginate is anionic polysaccharide occurring naturally in brown algae and has a unique property different from traditional antacids. Alginate and bicarbonate, usually contained in alginate-based formulations, interact with gastric acid to form a foamy gel, and this foamy gel, like a raft floating on the surface of gastric contents, creates a relative pH-neutral barrier. Alginate-antacid formulations can reduce postprandial symptoms by neutralizing the acidity of gastric contents and, more importantly, by forming a gel-like barrier to displace the "acid pocket" from the esophagogastric junction and protect the esophageal mucosa. Like antacids, alginate-based formulations demonstrate an immediate onset of effect within 1 hour of administration, faster than PPI and H2RA. Furthermore, alginate-based formulations have longer duration and higher efficacy than traditional antacids in relieving reflux symptoms, even in NERD patients. The mechanism of symptom relief in NERD patients treated with alginate is possibly related to protection of esophageal mucosal integrity. The other potential role of alginate in GERD patients is reducing the damaging of nonacid reflux, like pepsin and bile acids. A randomized double-blind double-dummy trial in moderate GERD patients showed that an

alginate-based formulation, Gaviscon (4×10 mL/day), was noninferior to omeprazole (20 mg/day) in achieving a 24 h heartburn-free period. Although alginate has less benefit in healing erosive esophagitis, it could be considered as an alternative or add-on therapy for symptom relief in GERD patients refractory to PPI. (24)

Therapy Focused on Mucosal Protection

Sucralfate

Sucralfate, a complex salt of sucrose sulfate and aluminum hydroxide, contributes to mucosal protection by several different actions. It provides a physical barrier to block diffusion of acid, pepsin, and bile acids across esophageal mucosa and attenuate the erosive injury of acid and alkali. The potential benefits of sucralfate include mucosa repair and ulcer healing. Sucralfate shows its efficacy in improving reflux symptoms in patients with reflux esophagitis and NERD patients. Like antacids and alginate, sucralfate has a limited role in healing of erosive esophagitis and is usually considered as add-on therapy for GERD treatment. For its low maternal adverse events and no teratogenicity, sucralfate is a safe drug for pregnant woman with reflux symptoms. (25)

Therapy Focused on Acid Suppression

Histamine Type-2 Receptor Antagonist (H2RA)

Before development of PPIs, H2RAs were the first acid-suppressive agents and have better efficacy than antacids in healing of erosive esophagitis and alleviating reflux symptoms. H2RA reduces gastric acid output as well as gastric acid volume by competitive inhibition of histamine at H₂ receptors and reducing pepsin secretion. However, patients with severe erosive esophagitis have poorer therapeutic response to H2RA, and most patients with GERD have only improved, but not eliminated, reflux symptoms after H2RA use. H2RAs also have their limitations in treating erosive esophagitis, such as their relatively short duration of action (compared with PPIs), development of tolerance, and incomplete inhibition of acid secretion in response to a meal. In meta-analysis, H2RAs are less effective than PPIs in healing of erosive esophagitis and relieving heartburn. (26)

Although H2RAs are not as effective as PPI in acid suppression, the potential effect of H2RAs on the nighttime histamine-driven surge in gastric acid secretion makes H2RAs an add-on therapy for patients with nighttime symptoms on PPI treatment such as nocturnal acid breakthrough (NAB). NAB is defined as a gastric pH < 4 for a period greater than 1 hour overnight in patients on twice-daily PPI therapy and occurs in more than 70% of patients on PPI therapy. Addition of a nighttime H2RA to twice-daily PPI can reduce the percentage of NAB and lead to an improvement of nighttime reflux symptoms and sustained efficacy in short-term and long-term use. There are no significant differences between different H2RA agents in suppressing gastric acid, and different H2RAs are

considered to have equivalent efficacy. At present, H2RAs are still popular over-the-counter medicines and widely used for controlling GERD symptoms because of their rapid onset of action. (27)

Proton Pump Inhibitor (PPI)

PPI blocks the gastric H⁺/K⁺-adenosine triphosphatase (ATPase) via covalent binding to cysteine residues of the proton pump to inhibit gastric acid secretion and is the most potent type of acid suppressants nowadays. (28) Inhibition of H⁺/K⁺-ATPase is more effective than antagonism of H₂R in suppressing gastric acid secretion because H⁺/K⁺-ATPase is the final step of acid secretion. Several trials and reviews have shown that PPIs are more effective in healing of erosive esophagitis and symptomatic relief than H2RAs. Eighty-three percent of patients with GERD symptoms and 78% of patients with erosive esophagitis have response to PPI treatment. Many studies have evaluated the efficacy or superiority between different PPIs (esomeprazole, lansoprazole, pantoprazole, and rabeprazole) and, the results were inconsistent. (29)

Potassium-Competitive Acid Blocker

Potassium-competitive acid blockers (P-CABs) are another class of acid suppressants developed in the last few years and inhibit proton pumps via a different mechanism than PPIs. By competing with binding of the potassium-binding site of proton pump, P-CABs reversibly inhibit gastric H⁺/K⁺-ATPase and do not require acidactivation, which means that they are mealtime-independent in contrast to PPIs. (30) P-CAB is absorbed very quickly and provides rapid and profound acid suppression by achieving peak plasma concentration rapidly. Several P-CABs such as revaprazan (YH1885), soraprazan, and AZD0865 have been evaluated in animal model and healthy volunteers, and these results have suggested that this group of acid suppressive drugs has a much faster onset of action and may provide greater acid suppression than conventional PPIs. However, initial clinical trials with AZD0865 did not show better results than conventional PPI in GERD treatment. In treatment of erosive esophagitis, AZD0865 once daily only provided similar efficacy to esomeprazole 40 mg once daily in healing and controlling symptoms of erosive esophagitis. In another clinical trial of AZD0865 and esomeprazole for the treatment of patients with NERD, AZD0865 also failed to demonstrate better heartburn control than esomeprazole in patients with NERD. Liver toxicity was also observed in several P-CABs during early stages of drug development. (31)

Therapy Focused on TLESR

TLESRs are defined as periods of spontaneous, simultaneous relaxation of the lower esophageal sphincter and crural diaphragm. Reflux of gastric content during TLESRs causes reflux symptoms, and TLESRs are the main mechanism of all types of gastroesophageal reflux, including acid and nonacid reflux episodes. TLESRs are primarily triggered by gastric distension through a

vagovagal reflex initiated by activation of mechanoreceptors in the cardiac of stomach. Several pharmacologic agents, including nitric oxide synthase inhibitors, cannabinoid agonists (CB1 receptor agonists), cholecystokinin receptor 1 (CCK1) antagonists, γ -aminobutyric acid type B (GABA_B) receptor agonists, and metabotropic glutamate receptor 5 (mGluR5) antagonists, have been developed as TLESR reducers. However, some of these compounds did not provide clinically relevant effect and demonstrated undesirable pharmacologic side effects in clinical trials. At present, only GABA_B receptor agonists and mGluR5 antagonists have reached the stage of clinical use and are the most promising agents of TLESR reduction. (32)

Surgical treatment:

Surgery may be recommended if you have serious GERD complications. For example, stomach acid can cause inflammation of the esophagus. This may lead to bleeding or ulcers. Scars from tissue damage can constrict the esophagus and make swallowing difficult.

Surgery for GERD is usually a last resort. Your doctor will first try to manage your symptoms with changes to your diet and lifestyle. This gives relief to most people with the condition. If that does not give you relief, they will try long-term medications. If these steps do not relieve the symptoms, then your doctor will consider surgery. You might also consider surgery to avoid taking long-term medications. (33)

There are several surgical options that may help to relieve GERD symptoms and manage complications. Speak with your doctor for guidance on the best approach to manage your condition.

If your GERD requires surgery, you should be sure and discuss the cost of your surgery with your doctor and the hospital. The costs vary greatly depending on your insurance, the hospital, type of surgery, and other factors.

Conclusion

GERD is defined as symptoms or complications occurring from the gastric reflux into the esophagus or beyond, into the oral cavity. Regurgitation or the backflow of gastric components into the mouth or chest. Refractory GERD cases commonly record atypical burning in the upper chest or throat. GERD is usually diagnosed clinically with classic symptoms and response to acid suppression. Upper GI series/barium swallows, upper GI endoscopy, esophageal pH monitoring, esophageal impedance-pH monitoring, ambulatory reflux monitoring, esophageal Bilitec, esophageal manometry, novel metrics, EGJ barrier function, oesophageal peristaltic function, provocative tests and optimization of GERD testing are effective diagnostic tools which used separately or in combination to precisely diagnose GERD. Life style modification and PPI therapy are the main stays of treatment for the majority of cases. Some patients may need endoscopic or surgical intervention

for relief of symptoms. The devices that produced to increase the lower esophageal sphincter is also effective in managing GERD.

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