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UPDATED GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

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Abstract

Background: 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 juice 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:

The American College of Gastroenterology (ACG) guidelines define gastroesophageal reflux disease (GERD) as "symptoms or complications occurring from the gastric reflux into the esophagus or beyond, into the oral cavity (including larynx) or lung" [1]. Erosive esophagitis (EE), non-erosive reflux disease (NERD), and Barrett's esophagus are the three phenotypic presentations of GERD [2].

GERD can be characterized as related to the erosions; GERD symptoms without erosions on endoscopic examination constitute non-erosive reflux disease (NERD), whereas GERD symptoms with erosions constitute erosive esophagitis (EE) [1]. It should be emphasized that EE can also occur in the absence of symptoms [3].

The determined GERD occurrence range was 8.7-33.1% in the Middle East [4]. Most of the Middle East studies done in Iran recorded 33%, while the Western ones reported 28%GERD occurrence [5]. In Saudi Arabia, in three studies carried in Riyad, the West region, and the South region, the prevalence of GERD was 45.4% and 23.47% and 15%, respectively [5, 6].

Lifestyle and risk factors for GERD have been described. GERD was observed to be more common in those who used non-steroidal anti-inflammatory drugs (NSAIDs) and those who were obese, smokers, and physically inactive [7]. Some food and drinks, like fast food, tea, coffee, carbonated drinks, and greasy food, are correlated to elevated prevalence of GERD [8].

Typical symptoms are heartburn and acid regurgitation. Extraesophageal symptoms include cough, laryngitis, asthma, or dental erosion. Atypical symptoms include dyspepsia, epigastric pain, nausea, bloating, and belching[1].

GERD is usually diagnosed clinically with classic symptoms and response to acid suppression. Heartburn with or without regurgitation is typically sufficient to suspect GERD, especially when these symptoms are worse postprandially or recumbent [9].

The management of GERD may involve food control, lifestyle modifications, medications, and operations. Primary management is usually done by a proton-pump inhibitor like omeprazole [1]. In some patients, a case with GERD signs can control them by using over-the-counter

medications [10]. This is safer and less costly than using prescription medications [10]. Some guidelines suggest managing GERD with an H2 antagonist before using a proton-pump inhibitor because of cost and safety concerns [10]. Diagnosis and treatment guidelines of GERD were published in 1995 and updated in 2005, and lastly reviewed in 2013by the American College of Gastroenterology (ACG). Here we aimed to review the latest updated guidelines of diagnosis and treatment of Gastroesophageal reflux disease (GERD).

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 GEDR, 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.

Pathophysiology

The lower sphincter of the esophagus is 3-4 cm long and composed of smooth muscles present at the distal portion of the esophagus [11]. Reflux is limited by this sphincter that produces immense pressure in between the esophagus and stomach. The relaxation of the lower sphincter usually provides reflux. Transient relaxation happens more commonly in GERD cases. Elevated calcium influx negotiated by the cholinergic neuron stimulates the sphincter to keep a larger tone than other structures. Resting sphincter has elevated intracellular calcium concentrations as compared to non-sphincteric esophageal muscles. Due to hiatus hernia, there is reduced pressure in the lower sphincter and reduced peristalsis in the distal esophagus, causing decreased refluxed acid removal. Late removal of gastric acid increases the gastric contents that stay there for a long time, thus increasing transient relaxations of lower sphincter muscles along with the gastric acid secretions. During sleep, the reflux episodes increase because of reduced swallowing of saliva, which neutralizes the gastric acid [12].

Symptoms

Refractory GERD cases commonly record atypical burning in the upper chest or throat unrelated to meals and correlated with belching, bloating, and dyspepsia [13]. Regurgitation or the backflow of gastric components into the mouth or chest [14] is also prevalent in refractory GERD but may be a symptom of rumination or gastroparesis disorder [15]. Alarm symptoms, like anorexia, odynophagia, dysphagia, anemia, weight loss, and gastrointestinal (GI) bleeding, must also be estimated. They may show more severe conditions, such as stricture formation [16] or upper GI malignancy.

Diagnosis depending on latest guidelines:

Symptom evaluation by clinical history and questionnaires

The first step in estimating refractory GERD is the description of determining symptoms and complicating factors. Typical symptoms are more probable than atypical ones to respond to therapy, indicating the value of an accurate clinical history [14]. Furthermore, surveys such as the reflux disease questionnaire (RDQ) and gastroesophageal reflux disease questionnaire (GERDQ) have similar limitations when compared with physiological testing [17].

Upper GI series/barium swallows

Barium radiographs are used to estimate cases with esophageal signs, but the test sensitivity is remarkably low [18]. It is not used in the routine diagnosis of GERD. However, it may be helpful in the setting of dysphagia [1].

Upper GI endoscopy

Upper GI endoscopy was recommended for persistent GERD signs despite PPI treatment optimization [1]. When it is done, biopsies should be gained to rule out EoE and esophageal malignancy [19]. Endoscopy can also recognize alternative causes of refractory signs, such as infectious esophagitis, caustic ingestion, BE, esophageal cancer, or gastric or duodenal ulcer [1].

Esophageal pH monitoring

Esophageal pH monitoring is a known diagnostic method for estimating cases with management-refractory GERD [20]. While the diagnostic outcome of pH monitoring in cases on PPI therapy is limited, it can recognize refractory GERD cases that might be helpful from additional PPI treatment and those whose signs are not correlated to residual acid reflux. Esophageal pH measuring in cases with atypical signs off therapy can resolve if reflux is the cause of their initial signs [20].

Esophageal impedance-pH monitoring

The ambulatory 24h esophageal impedance-pH estimation is registered in refractory GERD cases to recognize the use of non-acid reflux in persistent signs that do not respond to PPIs. It can identify excessive supragastric burping and rule out rumination when coupled with high-resolution manometry, but it cannot diagnose biliary reflux [21].

Ambulatory reflux monitoring

Ambulatory reflux monitoring can present confirming proof of GERD in cases with normal endoscopy, atypical signs, and/or when viewing ARS [22]. Reflux monitoring describes the result of GERD pathophysiology, manifest as either extreme oesophageal acid exposure time (AET) or reflux episodes, instead of the mechanism by which that happens. Reflux-symptom community practices simple ratios and statistical examinations to define whether reflux episodes co-happen with symptoms and gives power to ambulatory reflux monitoring. Therefore, reflux monitoring

can verify or exclude pathological GERD, although not always conclusively [22].

Esophageal Bilitec

Bilitec uses a sensor scaled on a catheter to recognize the distal esophagus's bilirubin appearance as a marker for bile reflux [23]. Usage of Bilitec to pH monitoring has been given to define the composition of reflux and improve the abnormal rate results by 30–40% in treatment-refractory cases [24]. It is not widely obtainable and needs special dietary restrictions [25].

Esophageal manometry

Esophageal manometry in refractory GERD has a limited benefit because most patients with treatment failure have NERD or a functional bowel disorder [14]. Nonetheless, esophageal manometry can be used for placing sensors before pH monitoring and for ruling out esophageal motor disorders or achalasia [26]. Manometry is also necessary for patients considering antireflux surgery, as up to 40% of patients with preoperative peristaltic dysfunction experience postoperative dysphagia [27].

Novel metrics

Two novel impedance-measuring parameters, the PSPW index and baseline impedance, have been examined within GERD phenotypes [28]. These metrics may increase the diagnostic value of impedance-pH testing, particularly in distinguishing GERD cases from those with functional heartburn [28].

In health, reflux episodes trigger the primary peristalsis to neutralize acidified oesophageal mucosa with saliva. This is evident as the antegrade progress of impedance decay within 30 s of a reflux episode (PSPW) on a pH-impedance study [28].

EGJ barrier function

The most fundamental abnormality in GERD is the incompetence of the EGJ as an antireflux barrier, making quantifying EGJ competence an attractive biomarker. However, the EGJ is a complex sphincter composed of both the crural diaphragm (CD) and lower oesophageal sphincter (LES), varying with circumstance. The EGJ pressure varies with time, respiration, and swallowing;, similarly, the EGJ morphology can also change over time, transitioning between superimposed and separated CD and LES elements [14]. Furthermore, some degree of EGJ incompetence is physiological, evident by the phenomenon of transient LES relaxation (TLESR), reflex relaxation of both the LES and CD that facilitates gas venting from the stomach [29].

Oesophageal peristaltic function

Oesophageal peristalsis can be characterized by the DCI, which summarizes post-transition zone contraction [30]. A DCI threshold of 450 mm Hg·cm·s correlates with an averaged distal peristaltic amplitude of 30 mm Hg [31], the original manometric threshold defining ineffective swallows. When abnormal, oesophageal peristalsis is often weak in GERD, with poor and/or delayed post-transition zone contraction segment [32].

Provocative tests

The physiological phenomenon of deglutition inhibition is more pronounced with multiple swallows in rapid succession. The esophagus remains in inhibition until after the final swallow, followed by a peristaltic contraction [33]. MRS and rapid drink challenge (RDC) are two provocative tests of deglutition inhibition integrity during HRM [34].

Optimization of GERD testing

GERD symptoms are diverse, response to treatment is variable, pathogenesis is heterogeneous and mechanistic phenotypes are heavily influenced by hypersensitivity and hypervigilance. Because simple algorithms starting with a PPI trial do not consider these complex phenotypes of GERD, they often lead to inappropriate PPI utilization, delayed diagnosis, and inaccurate diagnoses [35]. The Lyon Consensus opines that the optimal initial testing for PPI non-responders with no prior endoscopic or pH-meter demonstration of GERD is pH or pH-impedance monitoring done withholding antisecretory therapy. A key potential outcome of that testing is to rule out GERD and to redirect management towards weaning off PPIs, using neuromodulators and/or cognitive behavioral therapy as appropriate. In contrast, optimal testing in poorly responsive patients with a prior demonstration of GERD is the combination of EGD, HRM, and pH-impedance monitoring done on twice-daily PPI therapy. This combination of tests serves both to redirect treatment towards alternative diagnoses and to mechanistically subtype patients in terms of poor clearance, excessive reflux episodes, and hypersensitivity, each of which can trigger specific management options. The precise roles of baseline impedance, PSPW index, and provocative maneuvers on HRM remain clarified with future research [36].

Treatment:

GERD treatment requires a stepwise procedure. The purposes are to manage symptoms, to heal esophagitis, and to limit repetitive esophagitis or other complications. The treatment is based on non-pharmacologic treatment, pharmacologic treatment, and surgical treatment.

Non-pharmacologic treatment

Lifestyle modifications

Evidence shows that it is recommendable too, Lose weight in overweight and obese subjects, stop smoking, reduce alcohol consumption, raise the head of the bed, sleep in the left lateral decubitus position and avoid large food intake at least 2h before going to bed at night, especially if the subject has nocturnal symptoms [37].

There is no evidence for a general recommendation to eliminate foods that can trigger reflux symptoms, such as

spicy food, citrus fruit, foods with high-fat content, products with caffeine, and carbonated beverages [37]. If the patient finds that any of these foods are associated with their symptoms, eliminating them from the diet can be beneficial [37].

Pharmacologic Therapy

About 80% of cases have a recurrent but non-progressive form of GERD that is managed with medications.

- **Antacids**

Antacids were the approved medication in the 1970s and are still active in managing mild symptoms of GERD [1].

- **H2 receptor antagonists and H2 blocker treatment**

H2 receptor antagonists are the first-line factors for cases with moderate symptoms and grades I-II esophagitis. Choices involve cimetidine, famotidine, and nizatidine. The US FDA stated optional recalls of ranitidine from the pharmacies between December 2019 and February 2020 after growing principal attention in September 2019 about medication contamination with the carcinogenic molecule's impurities N-nitrosodimethylamine (NDMA) [38]. A total withdrawal of all ranitidine drugs was demanded in April 2020 [39].

H2 receptor antagonists are useful for healing only mild esophagitis in 70%-80% of GERD cases and giving support treatment to limit relapse. Tachyphylaxis has been recognized, recommending that pharmacologic tolerance can decrease the long-term efficiency of these medications [38].

Additional H2 blocker treatment has been reported to be effective in severe cases (especially those with Barrett's esophagus) that have nocturnal acid breakthrough [38].

- **Proton pump inhibitors**

PPIs are the most productive prescriptions available for managing GERD. These factors should be utilized only when this situation has been objectively reported. They have few side effects. But, data have revealed that PPIs can conflict with calcium homeostasis and increase cardiac conduction deficits. Long-term use of these drugs has also been correlated with bone breaks in postmenopausal females, chronic and acute kidney disorder, community-acquired pneumonia, and Clostridium difficile intestinal infection [40].

Usable PPIs involve omeprazole, lansoprazole, rabeprazole, and esomeprazole. In November 2013, the FDA recommended the first generic versions of rabeprazole sodium delayed-release tablets to manage GERD in adults and teenagers ages 12 and up. In clinical trials, the most usually described opposing reactions to rabeprazole were sore throat, infection, flatulence, and constipation in adults, and diarrhea, headache, and abdominal pain in adolescents [41].

The Agency for Healthcare Research and Quality (AHRQ) concluded that PPIs were superior to H2 receptor antagonists for resolving GERD symptoms at four weeks and healing esophagitis at eight weeks [42]. The AHRQ observed no opposition between individual PPIs to reduce symptoms at eight weeks. For symptom relief at four weeks, esomeprazole 20 mg was equivalent, but esomeprazole 40 mg superior to omeprazole 20 mg [41]. The impacts of PPI in obstructive sleep apnea in patients with GERD noticed a lack of definitive data [42].

- **Prokinetic medications and reflux inhibitors**

Prokinetic drugs are somewhat useful but only in mild symptoms; other cases usually need other acid-suppressing drugs, like PPIs. The adult regimen is metoclopramide, 10 mg/day orally. Long-term usage of prokinetic drugs may have severe, fatal complications and should be discouraged [1].

Surgical management of gastroesophageal reflux disease

Laparoscopic fundoplication

Laparoscopic fundoplication is done under general endotracheal anesthesia. Five short incisions are utilized. The stomach fundus is enclosed around the esophagus to produce a new valve at the esophagogastric junction level. The AHRQ found, based on limited proof, that laparoscopic fundoplication was as efficient as open fundoplication in reducing heartburn and regurgitation, enhancing the quality of life, and decreasing the use of antisecretory medications [41].

Sleeve gastrectomy

In research that estimated laparoscopic sleeve gastrectomy for GERD in 71 obese cases, symptomatic and reflux control improved most cases following the procedure [43]. But, it was reported that there were unable to define the impact of sleeve gastrectomy on the GERD prevalence owing to the high heterogeneity between the available studies and paradoxical results of objective esophageal function tests [44].

Devices

The US FDA recommended the LINX Reflux Management System in March 2012. This device is produced to increase the lower esophageal sphincter. The system is a small flexible band placed laparoscopically around the esophagus just above the stomach to produce a natural limit to reflux. The band is composed of interlinked titanium beads with magnetic cores. The swallowing action temporarily breaks the magnetic bond, allowing food and fluid to pass normally [45].

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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