Diagnosis and Treatment of Refractory Gastroesophageal Reflux Disease (GERD)

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ABSTRACT

Gastroesophageal reflux disease (GERD) was a damage in mucosal layer caused by gastric acid reflux. GERD was found about 10-20% in Western Countries and less in Asia, about 2,6-6,7%. Among different type of GERD, refractory GERD was a problem found in daily clinical practice. This terminology was used in patients with regurgitation and heartburn symptoms which is not responsive to 8 weeks proton pump inhibitor (PPI) therapy. There were several mechanisms underlying the etiology and pathophysiology of refractory GERD. In general, refractory GERD diagnosis was based on clinical findings, objective endoscopic examination, ambulatory reflux monitoring, and response to antiacid-secretion therapy. Reevaluation of patients compliance should be the first step in refractory GERD management. A further treatment strategies could be started, consist of medical and surgical therapies. A basic clinical knowledge of refractory GERD would help clinician in deciding the best approach for diagnosis and therapy.

Keywords: *refractory gastroesophageal reflux disease (GERD), proton pump inhibitor (PPI) therapy, diagnosis, therapy, reevaluation*

ABSTRAK

Gastroesophageal reflux disease (GERD) adalah kerusakan pada lapisan mukosa esofagus karena refluks dari asam lambung. Dari berbagai jenis GERD, refractory GERD menjadi salah satu permasalahan yang ditemui pada praktik klinis. Terminologi ini mengacu pada gejala regurgitasi dan rasa terbakar pada dada yang tidak membaik setelah terapi proton pump inhibitor (PPI) selama 8 minggu. Ada beberapa mekanisme yang diduga mendasari etiologi dan patofisiologi dari refractory GERD. Secara umum, refractory GERD didiagnosis berdasarkan manifestasi klinis, temuan objektif pada endoskopi, ambulatory reflux monitoring, dan respons terhadap terapi anti sekresi asam. Reevaluasi dari komplians pasien harus menjadi lini pertama dalam penatalaksanaan refractory GERD. Strategi tatalaksana lanjutan perlu dipikirkan, mencakup penatalaksanaan medikamentosa dan operatif. Pengetahuan dasar klinis yang baik akan membantu klinisi dalam menentukan pilihan yang tepat untuk melakukan diagnosis dan tata laksana dari refractory GERD.

Kata kunci: *refractory GERD, terapi proton pump inhibitor (PPI), diagnosis, terapi, reevaluasi*

INTRODUCTION

Gastroesophageal reflux disease (GERD) was a pathologic condition marked by mucosal damaged caused by reflux of gastric acid. GERD prevalence was estimated based on heartburn sensation and regurgitation symptoms in patients. A systematic review reported GERD prevalence in Western Countries as much as 10-20%.[1] Otherwise in Asia, GERD prevalence was lower, about 2,6-6,7%. This prevalence was increasing in recent years.[2] Heartburn symptoms was found in 2,5-4,9% of East Asia and South East Asia population. Several GERD complication is esophagitis and dysphagia, found in 3,4-16,4% of East Asia and South East Asia population.[3]

Symptoms related to GERD was heartburn in midsternum and regurgitation. Even dysphagia was found in GERD without complication, this symptoms raise the alarm of complication present, such as stricture, motility disorder, Barret's esophagus, and adenocarcinoma esophagus. GERD also could manifest as extraesophageal atypical symptom, such as non-cardiac chest pain, bronchial asthma, laryngitis, chronic cough, dysphonia, and pneumonia. Adequate GERD treatment could improve extraesophageal symptoms above. A study in Hongkong reported that GERD was found in 29% patients with chest pain symptoms but normal corangiogram. About 92% among them having abnormal pH during 24-hours monitoring, and well-respond to proton pump inhibitor (PPI) therapy. [4] A study in Japan showed that PPI therapy for 8 weeks will improve asthma symptoms in adult.[5] GERD therapy need a comprehensive approach, including life style changes and adequate medication therapy. Several condition was proofed to be the risk factors of this disease. Obesity, especially central obesity, was a risk factors of GERD incidence. A meta-analysis study showed that obesity was strongly correlated to GERD, erosive esophagitis, and adenocarcinoma esophagus.[6] The raise of intragastric pressure, transient esophagus sphincter relaxation, nutcracker esophagus, and non-specific gastrointestinal motility disorder underlie GERD pathogenesis in obese patients. High fat diet, alcoholism, smoking was also believed to increase heartburn and regurgitation risk, although objective data present a contradictive result.[7,8,9]

Gastric acid suppression was the main therapy for GERD. Although PPI was the best suppression agent, symptoms were found not improving in one third patients in intensive PPI therapy.[10] Refractory GERD was a condition where GERD symptoms were not improving after adequate PPI therapy. Other therapy such as histamine antagonist receptor, transient lower esophageal sphincter relaxation (TLESR) reducer, prokinetics, and alginate was an additional drugs in patients with PPI therapy. Another strategies besides PPI was still in development, especially for patients unresponsive to PPI.

ETIOLOGY AND PATHOPHYSIOLOGY

This disease has a wide clinical spectrum. GERD could manifest typically, atypically (extraesophagus manifestation), until severe complication such as Barret's esophagus and adenocarcinoma esophagus. Patients with regurgitation manifestation mostly did not present abnormalities in esophagus mucosa during endoscopic examination. This patients was categorized as non-erosive gastroesophageal reflux disease (NERD) or could be known as functional heartburn. NERD prevalence reach 70% in patients with regurgitation and heartburn symptoms.[11] NERD was potential to develop to erosive reflux disease (ERD) NERD and ERD differ from mucosal damage findings and other functional symptoms findings. Patients with NERD was not found any sign of mucosal break, esophageal sphincter disorder, and low acid exposure profile. But, this patients responds worse to PPI than ERD patients.[12] A lot of mechanism underlying the pathogenesis of GERD, such as transient lower esophageal sphincter/ TRLES), low pressure in lower esophageal sphincter (LES), and imbalance mucosal defence, esophageal clearance disorder, visceral hypersensitivity, hiatal hernia, and delayed gastric emptying.

Basically, GERD was a multifactorial condition involving LES contraction or the presence of TLESR. TLESR defined as LES relaxation spontaneously about 5 second without anterograde flow. Incompetence of antireflux system cause an exposure of esophagus with acid, bile, pepsin, and other pancreatic enzyme which can damage mucosal layer. LES tonus disorder was caused by several pharmacologic agents, hormonal therapy, and diets: cholesistokynin, progesterone, calcium channel blocker, nitrate, caffeine, and chocolate. Impaired mucosal defence system was also underlying pathogenesis of GERD. Failure of mucosal barrier immunity, via bicarbonate from salivary, impair hydrogen ion transport, and gastric distension will result in longer acid exposure to esophagus, thus trigger inflammation process.[13,14]

Other factors causing anterograde flow to esophagus was hiatal hernia. In this condition, proximal portion of gastric dislocate via diaphragm, so that this condition will impair LES function and increase the

risk possibility of refluxate in hiatal sac, and increase its possibility to regurgitate open LES, colicky pain. The mechanism proposed in hiatal hernia was the accumulation of deep refluxate in hiatal sac. This condition also have an impaired gastric acid clearance ability.[14]

Continuous exposure in esophageal mucosa with refluxate caused by impaired antireflux barrier and clearance luminal mechanism was the main factors of epithelial morphological changes in GERD patients. But, refluxate and bile acid indirectly damage mucosal layer by stimulating cytokine production which damage the epithelium itself. This was proven by the increase of cell permeability, shown by dilated intracellular space (DIS) found in NERD and ERD patients. This increase in cell permeability stimulate nociceptive neurons to emerge pain sensation.[13] Refractory GERD definition was still in debate. But, in daily practice, this terminology was used in patients with regurgitation and heartburn symptoms which is not responsive to 8 weeks PPI therapy. The main causes of refractory GERD are: (1) Functional pyrosis; (2) Bad PPI compliance; (3) Inadequate PPI dosage; (4) Misdiagnosis; (5) Drug-induced esophagitis; (6) Genotype variation; (7) Non-acid reflux; (8) Eosinophilic esophagitis (EoE); (9) Dermal autoimmune disease.

Functional pyrosis was defined as heartburn episodes without any evidence of gastroesophageal reflux, motility changes, and structural abnormalities. This condition was caused by visceral hypersensitivity that cause excessive esophageal perception in acidic stimulation. Pathophysiology of visceral hypersensitivity was complex, involving psychoneuroimmunologic interaction and also central and peripheral sensitivity. This hypersensitivity in several cases showed an improvement in response to tricyclic antidepressant and psychotherapy.[16] Refractory GERD could be also caused by inadequate PPI therapy and bad compliance. Inadequate PPI therapy combined with inappropriate consumption would not be effective, seen as refractory GERD. Esophagitis was also caused by several agent like aspirin, NSAID, doxycycline, ascorbat acid, potassium chloride, and other chronic consumed drugs.[16]

Reflux of weak acid and base was one of the etiology of GERD symptoms that is not responsive to PPI therapy. Weak acid was defined as refluxate with pH 4-7, while alkaline was defined as refluxate with pH > 7. pH-metry-impedance could confirm this condition. Treatment in this case was difficult enough. Surgical intervention (fundoplication) could be needed to treat reflux phenomenon caused by non-acid or weakly acid refluxate. Yet, there were no evidence to support that.[16] Several studies use GABA agonist (baclofen) as non-acidic gastroesophageal reflux treatment and showed an satisfying result. Otherwise, because works in central, neurological effect of GABA agonist could lead to several side effect such as sleepiness and dizziness.[17] Eosinophilic esophagitis (EoE) was characterized by gastrointestinal symptoms similar to GERD, with dysphagia and vomitus. This symptoms was caused by eosinophilia in esohagus that unresponse to acid-supressor drugs. In this patients, asthma and another allergic symptoms was found. Endoscopic findings showed white exudate in mucosa. But, definitive diagnosis was still using histopathology as gold standard. In pathologic examination, patients with EoE were presented 15-20 eosinophil for each microscope examination field.

DIAGNOSIS AND TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

GERD diagnosis was based on clinical findings, objective endoscopic examination, ambulatory reflux monitoring, and response to antiacid-secretion therapy. Symptoms of heartburn and regurgitation was the specific symptoms of GERD, and both could be the reason to start PPI therapy. One systematic review showed sensitivity of heartburn and regurgitation account for 62-96%.[18] In patients with specific symptoms, empirical PPI therapy could help to diagnose GERD. Endoscopy was not recommended for routine examination, and only indicated for patients with alarm symptoms. Esophageal mucosa visualization was one of the diagnostic tools to evaluate Barret's esophagus. Oesophagus maag duodenum (OMD) or barium swallow was recommended in patients complaining dysphagia to eliminate mechanical dysphagia possibility. Esophageal manometry was not recommended as first line diagnostic tool of GERD because of any esophageal muscle disorder was not indicate a GERD diagnosis. Otherwise, manometry could be used to eliminate achalasia and hypomotility disorder (such as systemic sclerosis) before surgical treatment. Ambulatory reflux monitoring was a test to identify abnormal acid exposure, reflux frequency, and symptoms related to reflux episodes.[19] The summary can be seen in Table 2.

Table 1. Approach to GERD diagnosis

Diagnostic Test	Indication	Highest level of evidence	Recommendation
PPI trial	Classic symptoms, no warning signs	Meta-analysis	Negative trial does not rule out GERD
Barium swallow	Not for GERD diagnosis. Use for evaluation of dysphagia	Case-control	Do not use unless evaluating for complication (stricture, ring)
Endoscopy	Alarm symptoms, screening of high- risk patients, chest pain	Randomized control trial	Consider early for elderly, those at risk for Barrett's, non- cardiac chest pain, patients unresponsive to PPI
Esophageal biopsy	Exclude non-GERD causes for symptoms	Case-control	Not indicated for diagnosis of GERD
Esophageal manometry	Preoperative evaluation for surgery	Observational	Not recommended for GERD diagnosis. Rule out achalasia/scleroderma-like esophagus preop
Ambulatory reflux monitoring	Preoperatively for non-erosive disease. Refractory GERD symptoms,GERD diagnosis in question	Observational	Correlate symptoms with reflux, document abnormal acid exposure or reflux frequency

GERD: gastroesophageal reflux disease; PPI: proton pump inhibitor

Most of GERD patients did not respond to PPI therapy was from NERD and functional pyrosis group. Patients with NERD that response to PPI therapy only 37%. In contrast, ERD patients showed a better response to PPI therapy, account for 56%.[20] In refractory GERD, etiology of PPI resistance should be investigated. The first thing to evaluate on refractory GERD patients was compliance and previous therapy strategy. PPI optimization, whether by dosage and regiment compliance, should be done in refractory GERD patients before got I more specific diagnostic approach. Approach to refractory GERd diagnosis was presented in Figure 1. Richter et al simplify refractory GERD approach based on endoscopic findings.[21]

Based on previous theory, treatment of GERD included medical and non-medical therapy. Life style changes becomes important in this situation.

A systematic review reported that cocoa consumption, tobacco, and soda will also reduce LES competency, besides alcohol, caffeine, and fatty diets.[22] But, several study comparing patients diets to GERD diagnosis reported a contradictive result. High body mass index increase GERD risk by several mechanism, and reduce in body weight will improve GERD symptoms.[6] Sleeping position with head elevation was also proven to improve GERD symptoms.[23] Step by step for refractory GERD treatment approach can be seen in following algorithm.

The first step in refractory GERD treatment is to reevaluate patient compliance during previous PPI

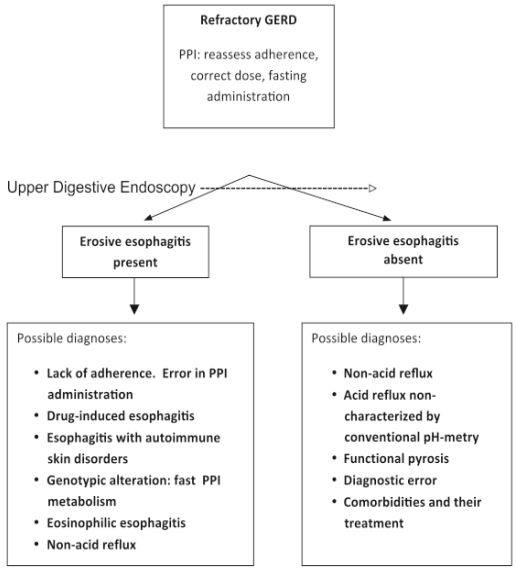

Figure 1. GERD diagnostic approach based on endoscopic findings[21]

Table 2. Non-medical treatment of GERD

Lifestyle intervention	Effect of intervention on GERD parameters	Sources of data	Recommendation
Weight loss	Improvement of GERD symptoms and esophageal pH	Case-control	Strong recommendation for patients with BMI > 25 or patients with recent weight gain
Head of bed elevation	Improved esophageal pH and symptoms	Randomized controlled trial	Head of bed elevation with foam wedge or blocks in patients with nocturnal GERD
Avoidance of late evening meals	Improved nocturnal gastric acidity but not symptoms	Case-control	Avoid eating meals with high fat content within 2-3 h of reclining
Tobacco and alcohol cessation	No change in symptoms or esophageal pH	Case-control	Not recommended to improve GERD symptoms
Cessation of chocolate, caffeine, spicy, foods, citrus, carbonated beverages	No studies performed	No evidence	Not routinely recommended for GERD patients. Selective elimination could be considered if patients note correlation with GERD symptoms and improvement with elimination

BMI: body mass index; GERD: gastroesophageal reflux disease

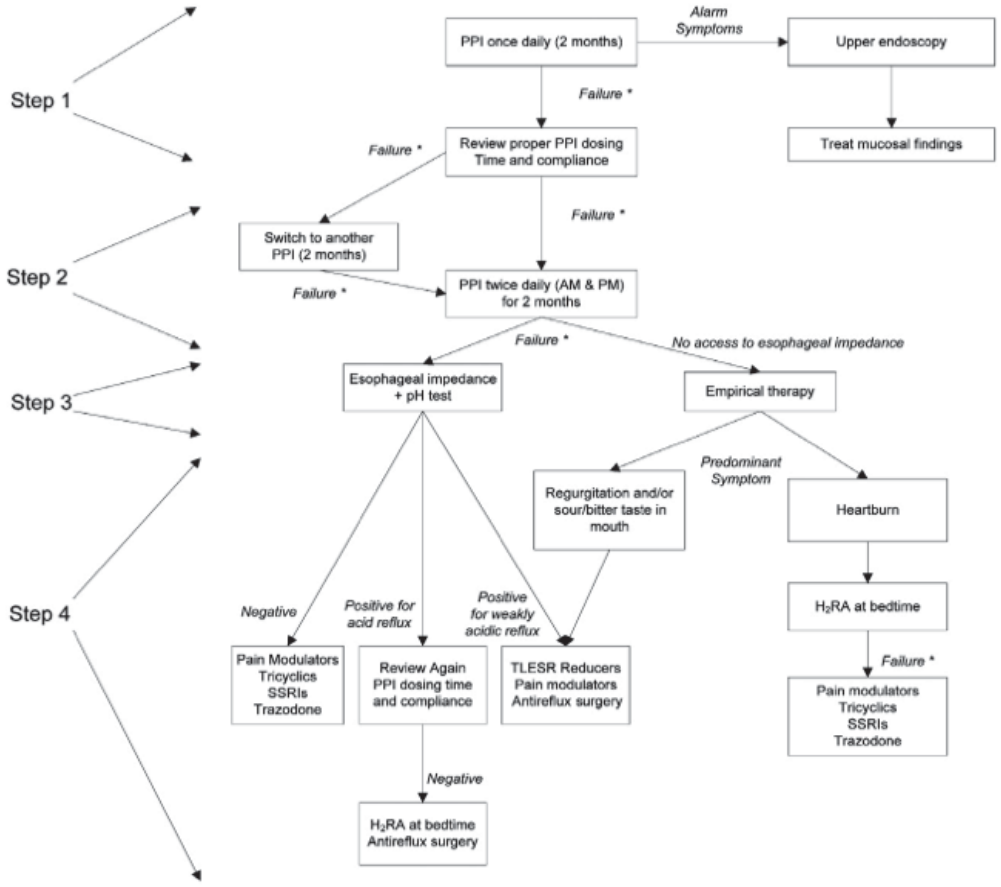

Figure 2. Steps in refractory GERD treatment

therapy. PPI therapy should be given 30 minutes before meals. Life style changes, have been mention above, should be emphasized to reach effective treatment outcome.[24] There are two options for patients that did not response to once daily PPI dosage, of which double its dosage or change to the other PPI regiments. Doubling PPI dosage was the most commonly used treatment strategy by clinicians. American College of Gastroenterology said that both strategies options could be used and proven to improve its outcome in reduce 20% of heartburn symptoms.[19,25]

Esophageal impedance and pH-monitoring, which can detect acid, weak acid, and alkaline, was the further approach in patients that did not respond to double dose PPI therapy. This test was also detect the correlation of symptoms to refluxate, and also its characteristic (gas, liquid, and mixed). This test could identify different etiology of GERD, either by acid, weak acid, alkaline, or functional pyrosis. A positive test result was the indication for TSLER inhibitor therapy, pain therapy, and surgical therapy. On the other hand, negative test result was the indication for pain therapy (selective serotonin reuptake inhibitors/SSRI or tricyclic antidepressant/TCA). Positive result for acid may indicated the need of therapy reevaluation. Reevaluation consist of PPI optimization, TLESR reducer, histamine antagonist receptor before sleep, and also surgical management. In healthcare service provider where esophageal impedance and pH-monitoring test was unavailable, symptoms characteristic could be the reason to give therapy. A dominant regurgitation symptoms indicated the need of TSLER reducer therapy, while a dominant heartburn symptoms indicated histamine-2 receptor antagonist therapy before sleep. If this regiment did not give an effective outcome, pain modulator such SSRI and TCA could be use. There were no evidence yet for giving antidepressant empirically in patients with refractory GERD.[24]

TSLER reducer showing the good outcome was GABA agonist such as baclofen. Adding 20 mg baclofen

three times per day together with omeprazole improves esophageal reflux frequency (p = 0,04).[17] Prokynetics therapy could be combined with PPI in patients with refractory GERD. Metoclopramide could increase LES tonus, esophageal peristaltic, and reduce gastric emptying time. But there were no study yet to prove that prokynetic given without gastroparesis in GERD patients could improves its symptoms. Metoclopramide and domperidone also gives side effect such as arrhythmia, and recommended to be stopped in patients with longer QT interval phenomenon. Antacid could be used as breakthrough therapy, but should not be given routinely as first line therapy in GERD patients. Sucralfat also could be added as adjuvant therapy because this aluminium chloride will give the protective effect to inflamed mucosal.

Surgical management as antireflux therapy was emerging in the last decades. There were two procedures available commercially, transoral incisionless fundoplication system (esophyx) and radiofrequency application. Esophyx used suction and transmural hooker to bind tissue in gastroesophageal junction to fundus and make a new valve/sphincter.[24] One prospective trail comparing laparoscopic antireflux surgery (LARS) and esomeprazole in refractory GERD. Five year remission was found in 92% patients with esomeprazole, and 85% found in LARS, but no significant differences. Both LARS and esomeprazole provide a good five years remission.[26]

Otherwise, Stretta procedure was a technique with endoluminal approach to give low radiofrequency energy in gastroesophageal junction. After radiofrequency application, it can be seen that LES was thickening and it could reduce TLERS frequency, reflux episodes, and also sensitivity to acid exposure.[24] This procedure have been proven to safe and give a good outcome result in improving gastroparesis, reduce gastric emptying period, and improve regurgitation symptoms in longer period.[27]

CONCLUSION

Gastroesophageal reflux disease (GERD) was a pathologic condition marked by mucosal damaged caused by reflux of gastric acid. GERD diagnosis was based on clinical findings, objective endoscopic examination, ambulatory reflux monitoring, and response to antiacid-secretion therapy. Symptoms of heartburn and regurgitation was the specific symptoms of GERD, and both could be the reason to start PPI therapy. The first step in refractory GERD treatment is to reevaluate patient compliance during previous PPI therapy. Esophageal impedance and pH-monitoring, which can detect acid, weak acid, and alkaline, was the further approach in patients that did not respond to double dose PPI therapy. Surgical management as antireflux therapy was emerging in the last decades. Stretta procedure have been proven to safe and give a good outcome result in improving gastroparesis, reduce gastric emptying period, and improve regurgitation symptoms in longer period.

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