THE IMPLICATION OF *MULTICHANNEL INTRALUMINAL IMPEDANCE* AND PH- MONITORING IN GERD PATIENTS

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ABSTRACT
Gastroesophageal reflux disease (GERD) is a prevalent condition caused by the retrograde flow of stomach contents into the esophagus, leading to troublesome symptoms and complications. Conventional diagnostic methods, such as proton pump inhibitor (PPI) trials and esophagogastroduodenoscopy, often fail to diagnose refractory GERD effectively. This study explores the utility of combined multichannel intraluminal impedance (MII) and pH monitoring for diagnosing refractory GERD in a 38-year-old female patient with persistent symptoms despite acid suppression therapy. A case study approach was utilized to evaluate the patient using impedance-pH monitoring, measuring reflux episodes, bolus clearance time (BCT), and proximal migration extent. The findings revealed 32 reflux events, primarily weakly acidic liquid reflux, and a DeMeester score of 31.38, indicating mild GERD. Proximal reflux and pathological BCT were identified, confirming refractory GERD. The diagnostic combination of impedance and pH-metry enabled a more precise assessment of reflux patterns, correlating symptoms with reflux events. This study underscores the limitations of standard GERD diagnostic approaches and highlights the advantages of advanced impedance-pH monitoring for refractory GERD. The findings emphasize the importance of personalized diagnostic methods for managing complex GERD cases, ensuring tailored treatment strategies. Further research is recommended to explore the broader applicability of impedance-pH monitoring in diverse GERD presentations. Its integration into clinical practice may enhance diagnostic accuracy and optimize therapeutic outcomes, addressing unmet needs in GERD management.
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INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as a pathological condition in which a retrograde flow of stomach contents back into the esophagus, and causes symptoms with or without complications (Liker, Ducrotté and Malfertheiner, 2009; Simadibrata *et al.*, 2011; Katz *et al.*, 2022). According to the 2006 Montreal definition, GERD is a condition of troublesome symptoms and complications that result from the reflux of stomach contents in to esophagus (Vakil, et al., 2006). GERD is one of the most common complaints in general medical practice and can be a debilitating condition requiring life-long medication. The global pooled prevalence of GERD was 20% and varied greatly according to region (18,1-27,8% in

United States of America and 9,8-25,9% in China) (El-Serag *et al.*, 2014). While GERD is a common disease and also the major upper gastrointestinal problem in Western countries, its prevalence amongst Asian has been reported to be relatively low, including Indonesia (Fock *et al.*, 2016). From the population-based studies, the prevalence of symptom-based GERD in Eastern Asia was found to be 3.5%-5% before 2000 and 4,3-15,7% after 2005. The true prevalence of GERD have revealed generally higher because of the ease get access to acid suppression drugs (Jung, 2011).

Currently, research on GERD in Surabaya revealed that more than half of dyspeptic patients in areas with low prevalence H. pylori could instead be associated with GERD (Miftahussurur *et al.*, 2018). The higher prevalence of GERD in areas with low H. pylori infection may be associated with acid reflux, smoking habits, history of using proton pump inhibitors, and higher economic class significantly increase the risk of GERD (Fock *et al.*, 2016; Miftahussurur *et al.*, 2018).

Clinical trial using proton pump inhibitors (PPIs) has been proven that this acid supressive therapy provides symptomatic relief that are not caused by gastric acid reflux as in GERD patients. It is reasonable that GERD and dyspeptic symptoms are manifestations of the same pathophysiology (Gerson, Kahrilas and Fass, 2011). The Rome III consensus proposed that people with functional dyspepsia symptomps, as the presence of at least one of the following reflux and retrosternal burning sensation rising up through the throat can be grouped into GERD disease (Geeraerts and Tack, 2008).

The classic and most common symptom of GERD are heartburn and acid regurgitation. Heartburn is a burning sensation in the chest, radiating toward the mouth, as a result of acid reflux into the esophagus. Acid regurgitation is a sour or bitter-tasting acid backing up into your throat or mouth (Kennedy and Jones, 2000; Moayyedi and Talley, 2006; Vakil *et al.*, 2006; Jung, 2011). Although classic symptoms of GERD are easily recognized, extraesophageal manifestations of GERD are also common but not always recognized. Extraesophageal symptoms can also manifest as atypical symptoms such as chronic cough, hoarseness, and globus sensation with a prevalence of 11%, 23%, 14%, respectively (Mainie, Tutuian, Agrawal, *et al.*, 2006; Forootan *et al.*, 2013).

The diagnosis of GERD is typically made by a combination of several modalities, including clinical symptoms, response to acid suppression treatment (PPI trial test), as well as objective evidence using esophagogastroduodenoscopy and esophageal pH monitoring (Forootan *et al.*, 2013). A new diagnostic approach using a combined multichannel intraluminal impedance (MII) procedure and pH-metric monitoring is recommended for patients with persistent and atypical GERD symptoms. The combination of using the pH- metry and multichannel intraluminal impedance in patients with refractory GERD is different from conventional pH, this is because this method provides a more complete evaluation of the relationship between symptoms and gastroesophageal reflux that occurs (Forootan *et al.*, 2013; Katz *et al.*, 2022). Based on the above explanation, we were interested in reporting a case of using combination of the pH-metry and multichannel intraluminal impedance as a diagnostic and monitoring tool in a 38-year-old woman with refractory GERD.

CASE REPORT

History Taking

A 38-year old female was admitted to the hospital with a chief complaint of abdominal pain and heartburn. Abdominal pain has been felt by the patient since 1 month ago and got worse 4 hours before entering the hospital. It was not affected by change position either when bending forward or supine. The patients complained that it got worsened after she consumed food and

drank coffee. In addition, she also complained of chest pain that felt hot and burning. The chest pain didn't radiate to the arms and neck, it also not accompanied by cold sweats or chest palpitations. The patient also complained of weight loss since 1 month ago, from 53 kg to 50 kg. The patient's appetite has been decreasing since 5 days ago, the last time she was only able to eat 2-3 spoons. The patient also complained difficulty swallowing food, frequent burping, and a bitter and sour taste on the tongue. No complaints when urinating and defecating. The patient had suffered epigastric pain and regularly visited the doctor and took sucralfat syrup and 40 mg/day of omeprazole since the previous year. The patient denied taking drugs for rheumatism or traditional drugs

On physical examination, the patient showed a general condition of weakness, with Glasgow coma scale (GCS) of 456, blood pressure of 125/75 mmHg, strong and regular pulse of 96x/minute, regular breathing of 20 x/m with rapid breathing pattern, axillary temperature of 36.5^{o}C. On the head examination, anemic conjunctiva and non jaundiced sclera were found. Heart and lung examination results were within normal limits. There was no abdominal and extremities abnormality. The laboratory results were as follows: Hb 9,6 gr/dl, hematocrit 31%, leukocytes 7,900/mm^3 (neutrophils 70%, lymphocytes 22%), platelets 333,000/mm^3, creatinine 0,8 mg/dl, BUN 6,0 mg/dl, albumin 4 gr/dl, SGOT 13,0U/L, SGPT 10,0 U/L, random blood sugar level 108mg/dL, kalium 3,51 mmol/l, natrium 138 mmol/l, chloride 106 mmol/l. HbSAg andHIV rapid test were non-reactive. The arterial bloodgas test (ABG) results were as follows: pH 7.38, pCO2 44.0 mmHg, pO2 89.0 mmHg, HCO3 23.7 mmol / L, BEecf -1 mmol/L, SO2 99%,temperature 37.0^{o}C. Chest X-ray examination in AP position showed that there were no visible abnormalities in the lungs and heart at that time.

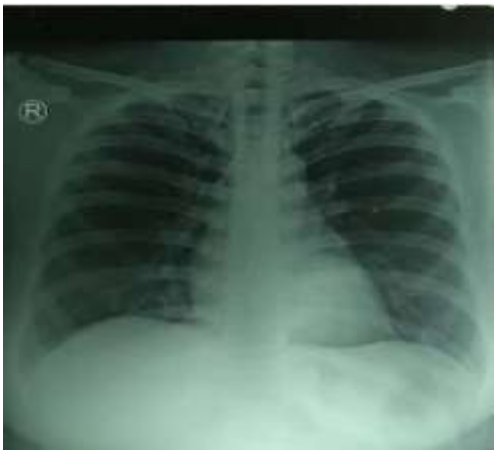


Figure 1

Initial Diagnosis was reported hypochromic Microcytic (Hb 9,6), suspect Chronic Gastritis, and Colitis. Ultrasonography, esophagogastroduodenoscopy, and *colonoscopy* were planned to support the diagnosis. The therapy included high calorie diet with high protein (1,2 g/kg/day); monitoring of fluid balance (input equals output), 1500cc of NaCl 0,9% infusion in24hours, acid suppression therapy injection per 12 hours, 15ml of oral sucralfate syrup every 8 hours, and oral probiotic sachet every 12 hours. The monitoring plan included monitoring of complaints, vital signs, urine production/24 hours.

Course of Disease and Diagnosis

On the 2nd day of treatment, the patient complained of weakness, accompanied by pain in the chest (feeling hot) and frequent bloating. It was found that the patient had vomitting which happened 2 times with a volume of 100 ml. The physical examination results were as follows:

GCS 456, blood pressure 106/60 mmHg, pulse 87x/minute, breathing 20x/minute, SpO2 99% on free oxygen. Therapy was added by intravenous injection of anti-emetics every 8 hours and ultrasound examination, esophagogastroduodenoscopy, and colonoscopy were performed. Abdominal ultrasound examination was performed with an impressive result within normal limits. The esophagogastroduodenoscopy showed an image of pan gastritis superficialis and sessile polyps in corpus. While, the colonoscopy showed an image of proctitis and suspect pan chronic colitis.

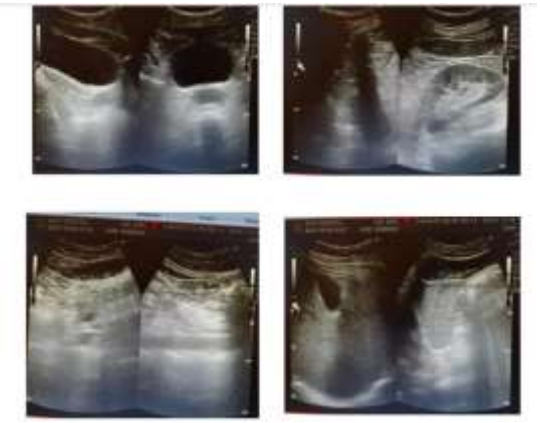


Figure 2

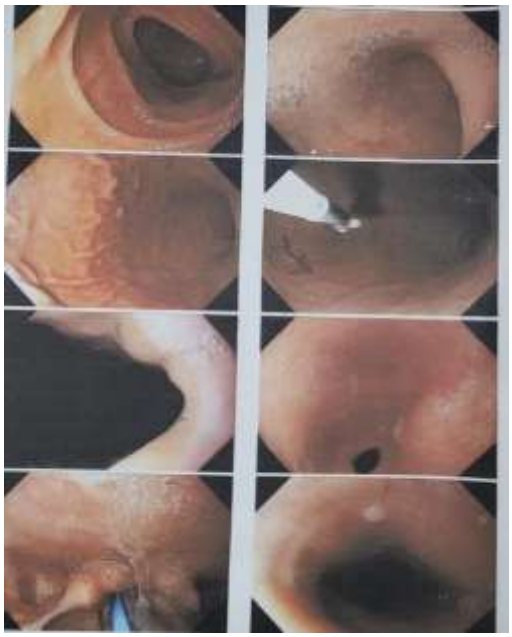


Figure 3

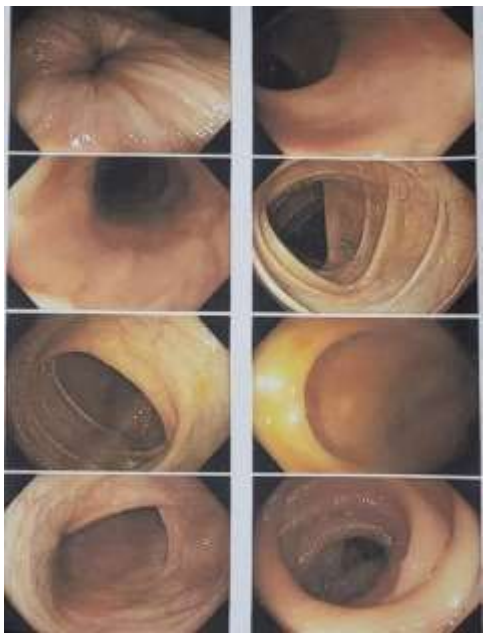


Figure 4

On the third day of treatment, the patient complained of weakness, the appetite still decreased, and a bitter taste in the throat. The physical examination results were as follows GCS 456, blood pressure 110/68 mmHg, pulse 91x/minute, breathing 20x/minute, SpO2 99% on free oxygen. On the fifth day of treatment, the patient said that still complained of frequent belching. The patient was able to defecate with normal volume and consistency. There was no blood during defecation. The physical examination results were as follows GCS 456, blood pressure 138/88 mmHg, pulse 92x/minute, breathing 20x/minute, SpO2 99% on free oxygen. Therapy with probiotic sachets and administration of drugs with acid suppression was discontinued. The patient is then measured with pH-metry along with monitoring multichannel intraluminal impedance.

Ph-Metry and Multichannel Intraluminal Impedance Examination Results

Impedance installation is placed at four measurement points in the distal esophagus, namely 3, 5, 7 and 9 cm and at two measuring points in the proximal esophagus, namely 15 and 17 cm above the LES (lower esophageal sphincter). Two pH sensors were placed at 5 cm above the LES margin (proximal sensor) and 15 cm at the proximal sensor in the stomach (distal sensor). This sensor position allows simultaneous pH analysis in the distal esophagus and stomach. The pH calibration was carried out before installation with a pH range between 4-7. Data recording is done for 24 hours. All reflux events that occurred were then analyzed, both in the upright and supine positions. Patients were instructed to press a button on the digital data recorder at the start of each symptom event. Patient subjects were also instructed to fill out cards regarding the time of consuming food, body position when symptoms occurred, and when symptoms occurred. There are no restrictions or prohibitions on the intake of food, drinks, and cigarettes. Based on the recorded impedance and pHmetry, the parameter values for the number of reflux episodes, bolus exposure time (BET), proximal extent migration, and bolus clearance time (BCT) will be obtained.

The total number of gastroesophageal reflux is 32 times. The incidence of reflux that caused by the movement of swallowing food was excluded 10 times, with the final result of gastroesophageal reflux was 22 times. Based on analysis the type of gastroesophageal reflux, it was found that liquid reflux occurred 17 times and mixed liquid-gas reflux occurred 5 times. In addition liquid reflux occurs with a pH that is classified as weakly acid, while for mixed liquid-gas reflux it is divided into 1 episode of acid reflux and 4 episodes of weakly acid. The recorded DeMeester Score is 31.38.

The patient had experienced 1 episode of proximal extent reflux in an upright position with the type of reflux was non-acid liquid. The bolus clearance time (BCT) experienced in the upright position occurred for 276 seconds (4.6 minutes) and in the supine position for 168 seconds (2.8 minutes). Both are classified as pathological MII. It was found that symptoms happened 5 times, with a total of 26 reflux. It can be concluded that there were 21 periods of reflux but did not cause any symptoms in the patient. Most of the reflux that occurs is classified as weakly acid reflux (pH range 4-7). The symptom index (SI) is 3.8. The patient then continued the treatment at the internal medicine clinic after 1 week was discharged from hospital with prescription of gastric acid-lowering syrup 15 ml every 8 hours orally and second-line acid suppression capsules at a minimum dose every 12 hours orally which were taken only if the patient felt symptoms.

RESULT AND DISCUSSION

Patients with typical GERD symptoms such as heartburn and acid regurgitation without alarm symptoms are recommended to use an empirical trial of therapy with a standard dose of a proton pump inhibitor (PPI) for at least 8 weeks as initial therapy (Jung, 2011; Katz *et al.*, 2022). As mentioned above patients with typical symptoms of heartburn and acid regurgitation have very high specificity (89% and 95%, respectively), although with low sensitivity (38% and 6%) to support the diagnosis of GERD (Vaezi, 2015; Katz *et al.*, 2022). PPI is used as the main treatment, because it has a superior effect in the symptomatic relief and mucosal healing of erosive esophagitis when compared to other drugs (Indonesian Society of Gastroenterology (ISG), 2011).

Mrs. M has typical symptoms of heartburn that feels hot and burning. It doesn't radiate to the arms and neck, also not accompanied by cold sweat or chest palpitations. The patient was treated with oral acid suppression therapy every 12 hours as a initial management.

The efficacy of acid suppression therapy is related to genotype of cytochrome P450 C19

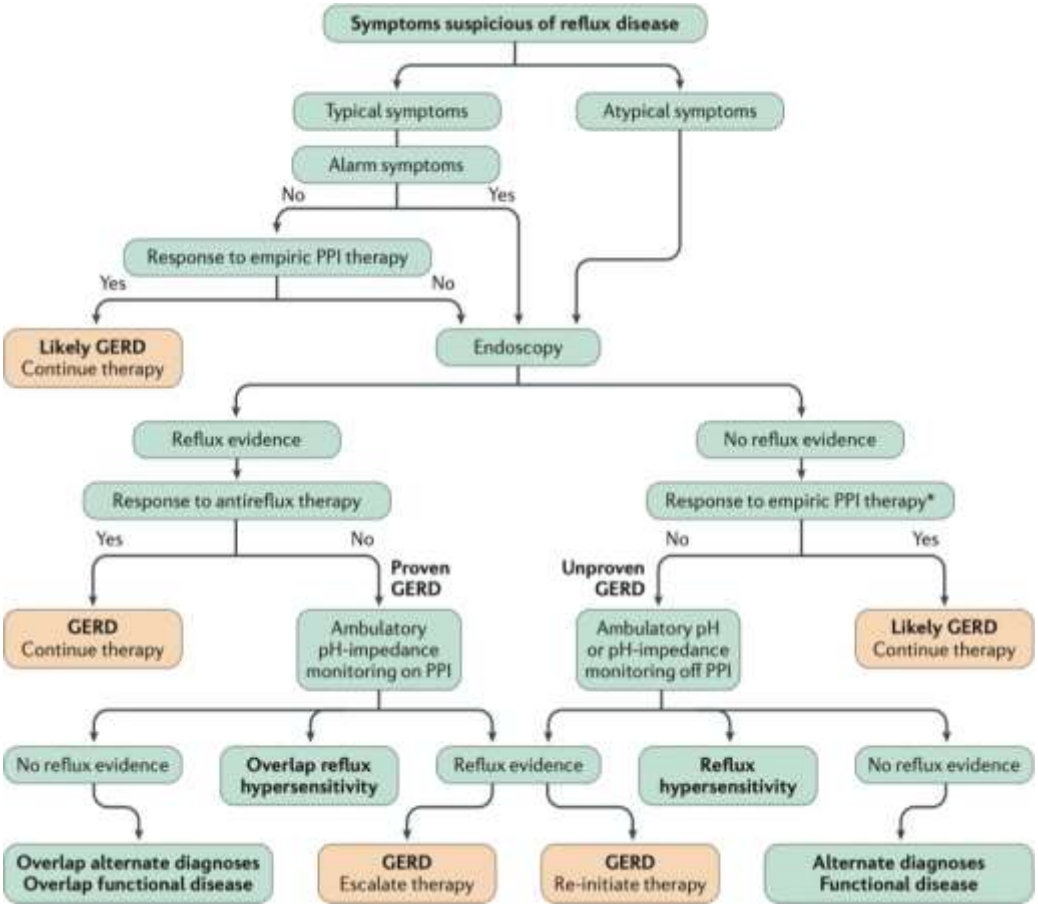
(CYP2C19) activity PPI dose, PPI treatment schedule, and timing of food intake (Junghard, Hassan-Alin and Hasselgren, 2002; Sugimoto *et al.*, 2012; Sugimoto *et al.*, 2014). The appearance of alarm symptoms or persistence of symptoms after 8 weeks empiric therapy in GERD patients is classified as refractory GERD (DeVault and Castell, 2005). A patient with a rapid metabolizer genotype of CYP2C19 re also considered to be at high risk of being refractory to PPI treatment (Ichikawa *et al.*, 2016). This group of patients is an indication for an EGD examination. EGD allows direct evaluation of the esophageal mucosa of GERD patients (DeVault and Castell, 2005; Fock *et al.*, 2008).

At the next treatment visit, the patient's complaints did not improve after using empirical therapy trials. She even said that there were additional complaints such as a weak body, bloated stomach, and feeling full when consuming food. The patient then underwent an additional examination of esophagogastroduodenoscopy.

Reflux disease is classified into GERD dan non – erosive reflux disease (NERD) (Long and Orlando, 2007). GERD is diagnosed based on the presence of mucosal damage or ulceration found during the EGD examination, while NERD is defined as the presence of reflux-related symptoms in the absence of esophageal mucosal damage or ulceration during GERD examination (Miftahussurur *et al.*, 2018). Although EGD have been used to diagnose GERD, the limitation of a gold standard has hampered the assessment of the accuracy of various approaches to the diagnosis of GERD. In addition, it is not known that most patients with typical symptoms typical of GERD have no evidence of esophageal mucosal damage (Vaezi, 2015). Approximately 25% of patients with GERD and 50% of patients with NERD are refractory to therapy with standard regimen doses of PPIs (Ichikawa *et al.*, 2016).

The results of EGD examination that was performed on Mrs. M shows that the lumen and peristalsis of the esophageal mucosa seem normal, no mucosal break at the gastroesophageal junction (GEJ) was found. On the 3rd day of treatment, the patient still had complaints and then the therapeutic management was replaced by injection of second-line acid suppression medication and the addition of intravenous antiemetic injections every 8 hours.

Ambulatory pH monitoring or multichannel intraluminal impedance is generally considered the diagnostic gold standard for use in patients with typical symptoms have no evidence of esophageal mucosal damage. The picture below describes the diagnostic algorithm in patients with symptoms suspected to be related with GERD (DeVault and Castell, 2005; Vaezi, 2015).



Picture. 5 Schematic of GERD

Generally, GERD is diagnosed clinically and treated with empiric therapy using a proton pump inhibitor (PPI) test. A PPI test is defined as the administration of a standard dose of PPI over a short period of 8 weeks to diagnose GERD (Gasiorowska and Fass, 2008). Improvement symptoms of heartburn and regurgitation after 8 weeks of administration is a reliable indicator of GERD. This approach has a sensitivity of 78% and a specificity of 54%, so a negative trial does not rule out GERD (Gawron *et al.,* 2012).

A new diagnostic tests using a combination of pH-metry procedures with multichannel intraluminal impedance can confirm or exclude the correct diagnosis of GERD. The pH-metry examination technique with multichannel intraluminal impedance is more sensitive to all types of reflux. This procedure is based on measuring the electrical impedance between electrodes that arranged close together on the intraluminal probe. The principle of impedance is inversely proportional to the intraluminal electrical conductivity and the cross- sectional area between the 2 electrodes. Baseline impedance values were obtained when there was no swallowing or reflux in the esophagus. This test has a range sensitivity value of 77% to 100% and a specificity of 85% to 100% (Ghoshal, 2016; Frongia *et al.*, 2022; Katz *et al.*, 2022).

During the pH impedance study, the amount of gastroesophageal reflux events detected was 32 times. The incidence of reflux caused by food was 10 times, so the final result of gastroesophageal reflux was 22 times.

Reflux monitoring can be performed in patients who are on or off the use of PPI therapy, however, reflux monitoring during PPI therapy is recommended in patients with a history of refractory GERD or as an indication for pH-metry tests to detect weak acid and non- acid reflux (Lechien, 2022). The type of gastroesophageal reflux are divided into 3 categories, namely liquid reflux, gas reflux, and mixed liquid-gas reflux. While bolus movements are divided into swallowing (antegrade) and reflux (retrograde) movements (Ghoshal, 2016). An empty

esophagus has an impedance of 2000 – 4000 Ω. Liquid reflux was considered as a retrograde fifty percent decrease in impedance from baseline in at least two distal impedance sites. The minimum duration of fluid reflux that could be calculated is 3 seconds. Gas reflux was identified as a rapid increase in impedance above 5000 Ω in at least two channels progressing distally to proximally. Mixed reflux (liquid– gas) was defined as gas reflux occurring simultaneously before or during a liquid reflux (DeVault and Castell, 2005; Ghoshal, 2016). Reflux episodes were identified according to previously described criteria and categorized to three groups including acidic (pH<4), weakly acidic (pH 4-7), non- acid (pH>7) (Forootan *et al.*, 2013).

The analysis based on the type of gastroesophageal reflux in patients found that liquid reflux occurred 17 times and mixed liquid-gas reflux occurred 5 times. As a conclusion liquid reflux occured with a pH that is classified as weakly acid, while for mixed liquid-gas reflux it is divided into 1 episode of acid reflux and 4 episodes of weakly acid.

A decrease in the esophageal pH value to <4 is conventionally defined as an episode of acid reflux. The cut off value is based on the fact that heartburn symptoms caused by esophageal acid perfusion in adults generally occur at pH <4 (Ebert and Greenberg, 2013). Furthermore, non-acidic substances, major proteolytic enzymes such as pepsin will not be active unless pH <4 (Kim, 2010).

Several parameters of esophageal reflux have been developed to assess the patient's condition including acid exposure, bolus exposure, and symptom index. *Acid exposure* (%) is defined as the total time during which the lower esophageal pH was below four divided by the duration of monitoring. Bolus exposure (%) is defined as being analogous to acid exposure by adding the duration of all reflux defined by impedance, and dividing this value by duration of monitoring (Ghoshal, 2016). While symptom index (SI) is defined as the number of symptoms associated with refl ux divided by the total number of symptoms. A value of SI ≥50 % is abnormal and is considered to diagnose GERD (i.e., at least half of symptoms are associated with reflux. SI is a parameter that is simple and easy to understanding (Cho, 2010; Ghoshal, 2016).

Several scoring systems have been developed to assess the patient's condition, including the DeMeester and Boix-Ochoa scores. However, the score does not include information about the relationship between reflux symptoms and there is no superior system for measuring the reflux index. The severity of symptoms does not correlate with the type of pathological acid reflux that occurs, so the range of normal values should be considered as a guide for data interpretation rather than as a reference absolute value (Bremner, 2020). DeMeester scores examined six variables, including number of reflux episodes, number of episodes longer than 5minutes, longest reflux duration, total percentage of monitoring time with pH below 4, and the percentage oftime with pHbelow 4 in an upright position and supine position. A score more than 14.72 was considered abnormal acid reflux, scores between 14.72 and 100 were regarded as mild-to-moderate GERD, and a score greater than 100 was regarded as severe GERD (Ghoshal, 2016; Liu *et al.*, 2017).

In this case, Mrs. M had a DeMeester score of 31.38 which was classified as mild Gastroesophageal Reflux Disease (GERD).

Based on the impedance recording with pH-metry, the parameter values for the number of reflux episode, bolus exposure time (BET), proximal extent migration, and bolus clearance time (BCT) will also be obtained. The proximal extent of reflux or reflux episodes that migrated proximally was defined as the level of fluid reflux as measured by impedance at 15 cm above the LES. The bolus clearance time (BCT) of reflux at 5 cm above the LES was defined as the time from 50% impedance drop to 50% impedance recovery. All reflux episodes were assessed in the upright and supine positions. Pathological MII was defined as the occurrence of fluid reflux than 32 times/day or gas reflux >17 times/day or mixed reflux >26

times/day. Bolus clearance time (BCT) components longer than 16 seconds/day or a proximal rate of more than 17 times over 24 hours are also classified as other components of pathological MII (DeVault and Castell, 2005; Zerbib *et al.*, 2006).

In this case, the patient had experienced 1 event of proximal extent reflux in an upright position with the reflux type was non-acid liquid. The bolus clearance time (BCT) in the upright position occurred for 276 seconds (4.6 minutes) and in the supine position for 168 seconds (2.8 minutes). Both are classified as pathological MII.

Combination of pH-metry and multichannel intraluminal impedance monitoring can strengthen the correlation between reflux incidence and symptom onset through the use of several analytical methods, including symptom index (SI), symptom sensitivity index (SSI), and possible symptom association (SAP). Symptom index (SI) 8 had the highest accuracy of 70.0% for diagnosing GERD with a sensitivity of 78.6% and specificity of 69.2%, followed by symptom index (SI) 3 had an accuracy of 62.1%, a sensitivity of 96.4%, and a specificity of 34.6%. The SI 3 reference has the highest sensitivity. While with the highest accuracy value, SI 8 is very useful for diagnosing GERD (Prakash Gyawali *et al.*, 2018).

In this study, patients experienced 5x symptoms, with a total reflux of 26 times. It can be concluded that there were 21 periods of reflux but did not cause symptoms in the patient. Most of the reflux that occurs is classified as weakly acid reflux (pH range 4-7). The symptom index (SI) is 3.8, which means it has the highest sensitivity with a moderate specificity value. Several potential diagnoses can also be identified related to pH-metry and multichannel intraluminal impedance measurements. Inadequate acid suppression can be caused by factors of patient adherence to drugs, the presence of CYP2C19 mutations, or due to the influence of residual acid reflux, weak acid reflux and alkaline. CYP2C19 mutations affect PPI metabolism to be rapid or slow *(*Prakash Gyawali *et al.*, 2018). However, the choice using combination of pH-metry with multichannel intraluminal impedance still has limitations. First of all, it is as invasive as traditional pH-metry and this reduces patient's compliance. This procedure also cannot evaluate the volume of esophageal reflux; takes almost 24 hours for data recording and costs are not cheap; records that are complex and may contain artifacts that interfere with interpretation; there is variability from day to day; and not always available in all health care centers in Indonesia (Ghoshal, 2016; Miftahussurur *et al.*, 2018).

CONCLUSION

The combination using pH-metry with multichannel intraluminal impedance provides important information for patients who are resistant to empiric GERD treatment. Until now, the impedance recording procedure and pH-metry provide several advantages, including information on parameter values for the quantity of reflux episodes that occurred, bolus exposure time (BCT), and reflux proximal extent. The indication using pH-metry with multichannel intraluminal impedance, including refractory GERD, GERD with atypical symptoms, preoperative evaluation, and to assess the type of reflux (acid vs non acid).

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