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REFRACTORY GERD IN CLINICAL PRACTICE: EXPLORING CHALLENGES AND ADVANCES IN TREATMENT

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ABSTRACT

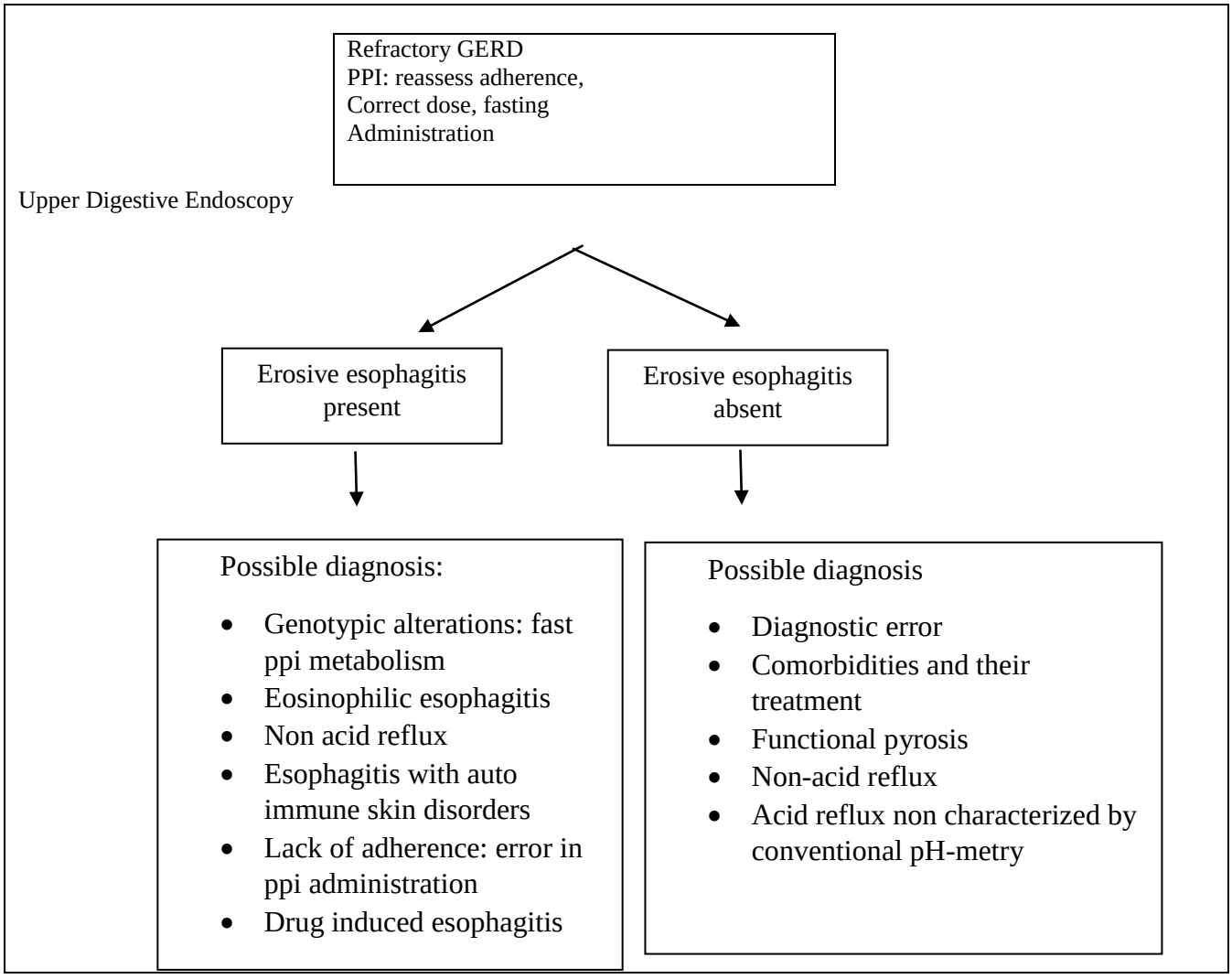
Background: The backward flow of stomach contents into the oesophagus is the hallmark of gastro-oesophageal reflux disease (GERD), a common disorder that causes symptoms including regurgitation and heartburn. A small percentage of people have refractory GERD, which is characterised by prolonged symptoms, even if the majority of cases improve after proton pump inhibitor (PPI) treatment. These cases provide difficult diagnostic and treatment problems. **Objective:** The purpose of this article is to examine the difficulties in identifying and treating refractory GERD, with an emphasis on the underlying mechanisms and new developments in management techniques. **Methods:** A thorough analysis of the available research was done, with an emphasis on the aetiology, methods of diagnosis, and available treatments for refractory GERD. The limitations of PPI medication, functional heartburn, esophageal hypersensitivity, and non-acid reflux are important research topics. **Results:** Refractory GERD is a complex disorder that can be caused by a number of different processes, such as increased sensitivity of the oesophagus, esophageal motility problems, and non-acid reflux. Improvements in diagnostic techniques, like high-resolution manometry and ambulatory pH-impedance monitoring, enable a more complex comprehension of the reflux burden. Beyond taking PPIs, there are now more treatment options for refractory GERD, including prokinetic drugs, endoscopic procedures, and surgery. The treatment of patients with esophageal hypersensitivity and functional heartburn also involves psychological therapies. **Conclusion:** In clinical practice, refractory GERD poses a difficult problem that calls for a customised diagnostic and treatment strategy. More study is required to completely understand the pathophysiology of refractory GERD and to create more potent, focused treatments, even with advancements in diagnostic technology and therapeutic alternatives. In order to maximise patient outcomes, multidisciplinary care that includes medical, endoscopic, and psychological therapies is essential.

KEYWORDS: Refractory Gastro Esophageal Reflux Disease, proton pump inhibitors, prokinetic agents, endoscopic therapy, treatment advances.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.[27] Gastro Esophageal Refractory Disease is charactized by the symptoms of heartburn and regurgitation. In gastroenterology practice today, the most common presentation of gastro-esophageal reflux disease (GERD) is failure of proton pump inhibitor (PPI) therapy in patients with conventional or atypical/extraesophageal presentations of GERD.[9] Every week, over one-third of adult's report experiencing the classic symptoms of GERD, which include regurgitation, heartburn, and esophageal chest pain.[8] GERD lowers job productivity and affects quality of life (HR-QOL). Therefore, regardless of whether mucosal breaks are seen during endoscopy or not, mild reflux symptoms that occur more than once per week lower HRQOL and can be classified as GERD.[7] GERD may be non-erosive or erosive. Erosive esophagitis (EE) is characterized by inflammation or ulceration of the esophagus brought on by reflux. Non-erosive reflux disease (NERD) is defined as having acid reflux measured by 24-hour ambulatory pH monitoring.[3] It's still quite difficult to manage GERD patients who are refractory. It is important to think about and customize both medical and non-medical therapy approaches for the appropriate patient population. Using a range of diagnostic methods, including wireless pH monitoring, intra-luminal impedance +pH sensors, Others, like capsules, might better guide treatment.[26] The challenges in the refractory GERD are functional heartburn, non-erosive

reflux disease, these are the challenges we face in our day to day life based on the signs and symptoms.[18] A small percentage of individuals have refractory GERD, which is characterised by symptoms that continue even after receiving the best possible treatment with proton pump inhibitors (PPIs). The majority of GERD cases respond to pharmaceutical treatments. When it comes to diagnosis and treatment, this illness poses serious clinical difficulties. The conversation that follows highlights new developments in treatment approaches and examines the main difficulties that physicians have when treating refractory GERD.[1] The first obstacle in treating refractory GERD is coming up with a precise and uniform definition of the illness. Patients who are unable to alleviate their symptoms with 4–8 weeks of twice-daily PPI medication at the recommended dosages are considered to have refractory GERD.[18] According to referenced articles, the continuation of symptoms may be caused by extra-esophageal manifestations, functional gastrointestinal diseases, or non-acid reflux, rather than an acid reflux that has not been successfully addressed. Clinicians must so carefully consider the potential of other diagnosis, such as psychological issues, eosinophilic oesophagitis, or problems of esophageal motility.[10]



PATHOPHYSIOLOGY OF REFRACTORY GERD

Multiple processes contribute to the etiology of GERD, such as decreased mucosal defense, delayed stomach emptying, and dysfunction of the lower esophageal sphincter (LES). Nevertheless, it is still unknown what specifically causes refractory GERD. Traditional explanations like acid reflux may not adequately account for the enduring symptoms in these patients. A number of theories propose different explanations, including as motility problems, esophageal hypersensitivity, and non-acid reflux.[2]

Patients may occasionally have more than one of these conditions, which makes management more difficult. Furthermore, the term "functional heartburn" has been used to describe people who have GERD-like symptoms but no indication of acid reflux. These patients frequently have normal pH readings, but their poor response to proton pump inhibitors (PPIs) makes care more difficult.[5]

Psychological factors such as Anxiety and Depression also plays an important role in the symptom persistence and further complicating Treatment.

DIAGONSTIC CHALLENGES

Refractory GERD is diagnosed after a thorough assessment of clinical symptoms and the ruling out other illnesses. The initial step is to confirm if GERD is present using endoscopy, symptom questionnaires, and, if necessary, ambulatory pH monitoring or impedance testing.[16]

Many individuals with refractory GERD have normal mucosa, therefore endoscopic assessment alone is insufficient, even though endoscopy may reveal oesophagitis. Moreover, non-acid reflux is becoming more well acknowledged as a significant cause of symptoms in refractory patients, yet pH testing may miss it.[31]

While esophageal impedance monitoring can identify non-acid reflux, esophageal manometry can uncover motility abnormalities that may be a contributing factor to symptoms. However, not all clinical settings have access to these tests, and they can be expensive, which could cause delays in diagnosis. Therefore, in order to properly diagnose and treat refractory GERD, a thorough, customised approach is essential.[26]

1. AMBULATORY PH MONITORING: When evaluating acid reflux, this is still the gold standard. However, it is limited in patients with non-acid reflux or those who do not display severe acid reflux throughout the testing time High-resolution manometry and impedance testing have become increasingly effective in detecting non-acid reflux and measuring esophageal motility.[16]

2. ENDOSCOPY AND BIOPSY: To rule out other esophageal disorders such Barrett's oesophagus or eosinophilic oesophagitis, upper gastrointestinal endoscopy can be helpful. Additionally, biopsy samples can yield important information on the existence of inflammatory changes.[18]

3. ESOPHAGEAL PH-IMPEDANCE TESTING: By detecting both acidic and non-acid reflux episodes, this sophisticated method provides a more complete picture of the reflux burden. When acid reflux is not the main cause, it is very helpful in refractory patients.[33]

CHALLENGES IN REFRACTORY GERD

There are various challenges and conditions that may influence the refractory GERD. They are the different layers of complexity that overlap with the conditions and may be seen in many patients.

1. FUNCTIONAL HEARTBURN

Functional heartburn, a condition where patients experience heartburn without evidence of acid reflux, is another important consideration in the differential diagnosis of refractory GERD. Functional heartburn can mimic GERD but does not respond to PPI therapy.[26] Functional heartburn has a complicated and poorly known pathophysiology of symptom development. But the primary mechanism seems to be esophageal hypersensitivity, which modifies the feeling of esophageal pain.[31]

2. NON EROSIVE REFLUX DISEASE(NERD)

The function of esophageal pH monitoring is one of the main obstacles in the diagnosis of NERD. Even though acid reflux can be verified as the cause of symptoms by 24-hour pH monitoring, this is not always the case for NERD patients, particularly when reflux episodes do not closely match the onset of symptoms. To identify non-acidic reflux, impedance-pH monitoring has been developed; however, this technique is not always accessible and can require a lot of resources.[26]

3. ESOPHAGEAL HYPERSENSITIVITY: The oesophagus becomes more sensitive to normal levels of acid, bile, or even air in certain patients with refractory GERD, a condition known as esophageal hypersensitivity.[34] This phenomenon can cause symptoms like heartburn or chest pain even when there isn't any noticeable reflux.

CHALLENGES IN MANAGEMENT

Accurately identifying the root cause of prolonged symptoms is one of the biggest obstacles in the treatment of refractory GERD. The "one-size-fits-all" approach is inadequate because there are numerous possible etiologies, ranging from functional problems to non-acid reflux. Using a combination of patient-centered therapy procedures and diagnostic tools, clinicians must adopt a customized strategy. Concerns over the safety of extended medication are also raised by the possible negative effects of long-term PPI use, such as osteoporosis, kidney disease, and vitamin B12 deficiency.[30]

ADVANCES IN TREATMENT

Although refractory GERD treatment is still clinically challenging, there is promise for improved management because to a number of novel approaches and developments.

1. NON ACID REFLUX MANAGEMENT

Managing non-acid reflux, which has been found to be a major cause of refractory symptoms, may be beneficial in circumstances where medication is not working. Since proton pump inhibitors cannot treat non-acid reflux, prokinetic medications (such as domperidone or baclofen) or fundoplication (in extreme situations) may be helpful.[21] Transient LES relaxations, a major source of non-acid reflux, have been effectively reduced by the GABA-B receptor agonist Baclofen. Drugs that increase esophageal motility, such as domperidone and baclofen, have demonstrated potential in treating refractory GERD

symptoms. A GABA-B receptor agonist called Baclofen decreases the short-term relaxations of the lower esophageal sphincter, which are believed to be a contributing factor to reflux episodes.[20]

2. PPI THERAPY OPTIMISATION

PPIs are still the first-line treatment for GERD, but they frequently don't work well for refractory cases. Optimising PPI therapy is crucial in these situations. This entails making certain that the dosage, timing, and length of therapy are all acceptable (preferably 30 minutes before meals). Higher-dose PPI regimens may be advantageous for certain individuals, especially those who have experienced more severe exposure to esophageal acid.[22] Furthermore, methods like "titration" in PPI therapy—which involves modifying the dosage in response to symptom improvement—may offer more specialised treatment.

3. ENDOSCOPIC THERAPIES

For GERD instances that are not improving with surgery, endoscopic methods are becoming more and more popular. Transoral incisionless fundoplication (TIF) and radiofrequency ablation (e.g., Stretta treatment) are two techniques that have been developed to alleviate persistent problems. By applying radiofrequency radiation to the LES and gastric cardia, the Stretta technique may enhance LES tone and lessen reflux episodes. By creating a functional valve at the gastro-oesophageal junction, TIF, a minimally invasive surgery, restores the barrier against reflux.

Although the long-term results are still uncertain, a recent comprehensive analysis found that endoscopic therapies such as Stretta and TIF can be useful in lowering symptoms and enhancing quality of life in individuals with refractory GERD.[25]

4. PSYCHOLOGICAL INTERVENTIONS

Cognitive-behavioral therapy (CBT) is one psychological intervention that has showed promise in improving outcomes for individuals with refractory GERD, as it is increasingly recognised that psychological issues, including as anxiety and depression, may exacerbate GERD symptoms. According to a recent study, CBT can help GERD patients—especially those with functional heartburn—significantly reduce their symptoms and enhance their quality of life.[29]

5. SURGICAL TREATMENT: FUNDOPLICATION

In patients with severe, refractory GERD who do not improve with endoscopic or pharmaceutical treatments, surgery can be necessary. For surgical treatment, laparoscopic fundoplication is still the gold standard. This process prevents reflux by strengthening the LES. However, there are hazards involved, like bloating and dysphagia. Newer versions of the process are designed to minimise these issues without sacrificing effectiveness.[32]

6. LIFE STYLE MODIFICATIONS

The precise benefit of lifestyle changes for GERD patients who did not respond to PPI therapy is still unknown. The authors of a new systematic analysis of all the studies that assessed the benefits of lifestyle changes for GERD patients came to the conclusion that the only things that can effectively improve GERD are dietary interventions, weight loss and bed elevation.[28] For overall health benefits, quitting alcohol and tobacco usage should be taken into consideration in addition to weight loss. Although alcohol usage should be limited since it may trigger esophageal symptoms in certain patients.[25]

FUTURE DIRECTIONS

A greater emphasis on personalized medicine is indicated by the changing landscape of refractory GERD treatment. The pathophysiology of GERD may be better understood through genetic and molecular research, which could lead to new therapeutic targets like biologics that target particular pathways that cause inflammation brought on by reflux. Furthermore, the development of non-invasive tests for non-acid reflux and other improvements in diagnostic technology may make it possible to identify refractory cases more precisely and effectively.

LITERATURE SEARCH STRATEGY

We conducted a systematic literature review with search strategy based on Cochrane library. The databases searched are Pubmed, Science Journal and Gastroenterology journals. A two phased search strategy was performed with an intial search to establish primary search terms followed by a Second systematic search in all relevant data bases using the searching terms This search was conducted to identify the primary articles and studies on Refractory GERD challenges and advances in the treatment. Studies which were published from 1995 were searched and collected. A Systematic search of the literature was also conducted to identify relevant systematic reviews.

CONCLUSION

Refractory GERD is still a difficult condition to diagnose and treat in clinical practice, necessitating a multifaceted approach. Although PPIs are the mainstay of treatment, considering non-acid reflux causes and optimising PPI dosage may have further advantages. New treatments for this hard-to-treat group, such as endoscopic operations, psychiatric therapy, and non-acid reflux care, offer promise for better results. In order to improve management techniques and patient care, more study on the pathogenesis and therapy of refractory GERD is necessary. Refractory GERD remains a complex and multifactorial condition that poses significant challenges to clinicians. Advances in diagnostic methods and treatment modalities offer hope for improving outcomes for these patients, but a comprehensive, individualized approach remains essential. Further research into the

mechanisms underlying refractory GERD will be critical to developing more effective and targeted therapies.

REFERENCES

1. Dellon ES, Shaheen NJ. Persistent reflux symptoms in the proton pump inhibitor era: the changing face of gastroesophageal reflux disease. Gastroenterology, 2010 Jul 1; 139(1): 7-13.
2. Kahrilas PJ, Pandolfino JE. Pathophysiology of gastroesophageal reflux disease. Surgical Management of Benign Esophageal Disorders: The" Chicago Approach", 2014; 11-24.
3. Subramanian CR, Triadafilopoulos G. Refractory gastroesophageal reflux disease. Gastroenterology report., 2015 Feb 1; 3(1): 41-53.
4. Gyawali CP. Proton pump inhibitors in gastroesophageal reflux disease: friend or foe. Current gastroenterology reports, 2017 Sep; 19: 1-0.
5. Gabbard S, Vijayvargiya S. Functional heartburn: An underrecognized cause of PPI-refractory symptoms. Clev Clin J Med., 2019 Dec 1; 86(12): 799-806.
6. Richter JE. The patient with refractory gastroesophageal reflux disease. Diseases of the Esophagus, 2006 Dec 1; 19(6): 443-7.
7. des Varannes SB, Coron E, Galmiche JP. Short and long-term PPI treatment for GERD. Do we need more-potent anti-secretory drugs? Best practice & research Clinical gastroenterology, 2010 Dec 1; 24(6): 905-21.
8. Davis TA, Gyawali CP. Refractory Gastroesophageal Reflux Disease: Diagnosis and Management. Journal of Neurogastroenterology and Motility, 2024 Jan 1; 30(1): 17.
9. Fass R, Gasiorowska A. Refractory GERD: what is it?. Current gastroenterology reports, 2008 Jun; 10(3): 252-7.
10. Richter JE. How to manage refractory GERD. Nature Clinical Practice Gastroenterology & Hepatology, 2007 Dec; 4(12): 658-64.
11. Hershcovici T, Fass R. An algorithm for diagnosis and treatment of refractory GERD. Best practice & research Clinical gastroenterology, 2010 Dec 1; 24(6): 923-36.
12. Patel A, Yadlapati R. Diagnosis and management of refractory gastroesophageal reflux disease. Gastroenterology & hepatology, 2021 Jul; 17(7): 305.
13. Moraes-Filho JP. Refractory gastroesophageal reflux disease. Arquivos de gastroenterologia, 2012; 49: 296-301.
14. Naik RD, Meyers MH, Vaezi MF. Treatment of refractory gastroesophageal reflux disease. Gastroenterology & Hepatology, 2020 Apr; 16(4): 196.
15. Spechler SJ. Refractory gastroesophageal reflux disease and functional heartburn. Gastrointestinal Endoscopy Clinics., 2020 Apr 1; 30(2): 343-59.
16. Rettura F, Bronzini F, Campigotto M, Lambiase C, Pancetti A, Berti G, Marchi S, de Bortoli N, Zerbib F, Savarino E, Bellini M. Refractory gastroesophageal reflux disease: a management update. Frontiers in medicine, 2021 Nov 1; 8: 765061.
17. Roman S, Mion F. Refractory GERD, beyond proton pump inhibitors. Current Opinion in Pharmacology, 2018 Dec 1; 43: 99-103.
18. Fornari F, Sifrim D. Diagnostic options for patients with refractory GERD. Current gastroenterology reports, 2008 Jun; 10(3): 283-8.
19. Scarpellini E, Ang D, Pauwels A, De Santis A, Vanuytsel T, Tack J. Management of refractory typical GERD symptoms. Nature Reviews Gastroenterology & Hepatology, 2016 May; 13(5): 281-94.
20. Quigley EM. Prokinetics in the management of functional gastrointestinal disorders. Journal of neurogastroenterology and motility, 2015 Jul; 21(3): 330.
21. Ates F, Francis DO, Vaezi MF. Refractory gastroesophageal reflux disease: advances and treatment. Expert Review of Gastroenterology & Hepatology, 2014 Aug 1; 8(6): 657-67.
22. Dutta AK, Jain A, Jearth V, Mahajan R, Panigrahi MK, Sharma V, Goenka MK, Kochhar R, Makharia G, Reddy DN, Kirubakaran R. Guidelines on optimizing the use of proton pump inhibitors: PPI stewardship. Indian Journal of Gastroenterology, 2023 Oct; 42(5): 601-28.
23. Yadlapati R, DeLay K. Proton pump inhibitor–refractory gastroesophageal reflux disease. Medical Clinics, 2019 Jan 1; 103(1): 15-27.
24. Herregods TV, Troelstra M, Weijenborg PW, Bredenoord AJ, Smout AJ. Patients with refractory reflux symptoms often do not have GERD. Neurogastroenterology & Motility, 2015 Sep; 27(9): 1267-73.
25. Xie P, Yan J, Ye L, Wang C, Li Y, Chen Y, Li G. Efficacy of different endoscopic treatments in patients with gastroesophageal reflux disease: a systematic review and network meta-analysis. Surgical endoscopy, 2021 Apr; 35: 1500-10.
26. Domingues G, Moraes-Filho JP, Fass R. Refractory heartburn: a challenging problem in clinical practice. Digestive diseases and sciences, 2018 Mar; 63: 577-82.
27. Jie C, Junying X, Yong X, Xiaoping X, Cuiqiong Y, Xiaohua H. Analysis on the causes for refractory GERD. Journal of Huazhong University of Science and Technology [Medical Sciences], 2002 Mar; 22: 47-9.
28. Fass R. Therapeutic options for refractory gastroesophageal reflux disease. Journal of gastroenterology and hepatology, 2012 Apr; 27: 3-7.
29. Guadagnoli L, Yadlapati R, Pandolfino J, Bedell A, Pandit AU, Dunbar KB, Fass R, Gevirtz R, Gyawali CP, Lupe SE, Petrik M. Behavioral Therapy for Functional Heartburn: Recommendation Statements. Clinical Gastroenterology and Hepatology, 2024 Mar 20.

30. McCloy RF, Arnold R, Bardhan KD, Cattan D, Klinkenberg-Knol E, Maton PN, Riddell RH, Sipponen P, Walan A. Pathophysiological effects of long-term acid suppression in man. Digestive diseases and sciences, 1995 Feb; 40: 96S-120S.
31. Roman S. Gastro-esophageal reflux disorders. InClinical and Basic Neurogastroenterology and Motility, 2020 Jan 1; 225-236. Academic Press.
32. Frazzoni M, Piccoli M, Conigliaro R, Frazzoni L, Melotti G. Laparoscopic fundoplication for gastroesophageal reflux disease. World journal of gastroenterology: WJG., 2014 Oct 10; 20(39): 14272.
33. Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut., 2004 Jul 1; 53(7): 1024-31.
34. Gyawali CP. Esophageal hypersensitivity. Gastroenterology & hepatology, 2010 Aug; 6(8): 497.