ORIGINAL PAPER

THE ROLE OF 24-HOUR AMBULATORY PH-METRY AND MANOMETRY IN THE DIAGNOSIS OF NON-EROSIVE GASTROESOPHAGEAL REFLUX DISEASE

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ABSTRACT

Considered to be the pathology of the 21st century, gastro-esophageal reflux disease (GERD) still poses problems of diagnosis and treatment, especially in patients with atypical symptoms. The use of esophageal manometry and 24-hour pH monitoring, especially in the case of candidates for surgical treatment, allows the identification of patients who actually benefit from this type of therapy. We analyzed a group of 65 patients investigated for typical and atypical symptoms of reflux, in which endoscopy was normal and did not respond to treatment with PPIs (proton pump inhibitors) at the maximum dose. The patients were investigated by esophageal manometry and 24-hour pH metry and the characteristics of the batch and the results of the investigations were analyzed descriptively and statistically. Most patients were in the 51-60 age group, with a slight predominance of females. During the 24 hours monitoring, there were 14 patients who showed no symptoms, and of those who reported symptoms, only 37% actually had pathological acid reflux, as demonstrated by a DeMeester score >14.7. Another 3 patients had a symptom-reflux correlation >50%, but a DeMeester score <14.7, being included in the subtype of patients with hypersensitive esophagus. 24-hour Ambulatory Ph-metry in our group showed that only one third (34%) of patients with negative endoscopy and no response to PPI treatment have reflux disease. These patients may benefit from surgery as a therapeutic option.

KEYWORDS: *gastro-esophageal reflux, esophageal manometry, 24-hours pH-metry, proton pump inhibitors*

INTRODUCTION

Considered to be the disease of the 21st century, the very definition of gastro-esophageal reflux disease is a sum of contradictions. Although the concept involves the presence of typical symptoms, they are asymptomatic patients, diagnosed directly with severe complications such as Barrett's esophagus or esophageal adenocarcinoma. An abnormal 24-hour pH-metry result certifies the presence of pathological acid reflux, but the academic community interprets the association between the amount of reflux and the induced pathology as imperfect.

Equally, although it is defined by the presence of reflux esophagitis, the term "non-erosive reflux disease" is also fully accepted.

The pathogenesis of gastroesophageal reflux is a complex process, increasingly analyzed and challenged a process that is in a continuous reform and, yet, still completely unexplained. A number of theories have been circulated over time, ranging from the relaxation of diaphragmatic pillars or musculoskeletal structures, changes in the angle of implantation of the cardia, the theory of phreno-vertebral angle and theories on the relative pressures of the lower esophageal sphincter (LES). Today, endogenous factors are also added.

The symptoms of reflux pathology are manifested under a wide spectrum, the most common symptoms being heartburn, chest pain, acid regurgitation and belching. Other extraesophageal [1] symptoms include laryngitis, pharyngitis, chronic sinusitis, tooth erosion, asthma or chronic cough, depending on the ability of acid reflux to affect adjacent organs.

European statistics [2] discuss the way in which reflux pathology is felt at the social level: it reduces productivity by 26% in daily life, costs of absenteeism from work of 1 billion euro, losses for employers of 3 billion euro, the most affected being the German health system whose costs with GERD reach 4.8 billion.

In Romania, although there is no National Register of patients with reflux disease, some of the specialized research even supports a prevalence of GERD of 35% [3] in certain areas of the country. And the numbers are rising.

The latest OECD report "Romania. The Health Profile in 2017" [4] outlines some important directions in health, indicating the picture of the patient likely to develop reflux disease over time: 19.8% of adults smoked every day and more and more young people start smoking (increasing rate by 17%). Alcohol consumption reaches 53% among men, the highest average in the European Union, while the obesity rate is rising, with 9.1% of adults facing this problem.

Moreover, data on drug use speak for themselves. In the top 10 medicines dispensed through open circuit pharmacies, on the basis of medical prescription, in the social health insurance system, we find omeprazole with a settled value of 19,237,851 lei [5]. Other studies, such as those of OTC drugs, allocate a third place in the top of over-the-counter drugs, after cough, cold and allergy medication, consumption of 160.6 million lei and a market share of 18,2% [6].

In this context, this article finds its place. The pathology of reflux disease is important both in terms of affecting the quality of life and in terms of the risk of developing dreaded complications in the medium and long term such as Barrett's esophagus or adenocarcinoma. We must not forget the complications induced by the long-term treatment with proton pump inhibitors which, administered in the absence of a correct diagnosis, are not bringing benefits and may decompensate other chronic diseases.

Also, not infrequently, surgeons are dealing with patients with symptoms of reflux, without response to medical treatment, requiring for surgery. Surgical treatment is effective in the case of non-erosive reflux disease only after an accurate diagnosis. Otherwise, the surgeon may become the source of the patient's further problems.

Therefore, we consider that the earliest and most correct diagnosis of pathological reflux can lead both to avoid complications and to reduce the costs related to the treatment of a non-existent reflux disease.

MATERIALS AND METHOD

The present study is a retrospective one, the data of the research being part of the archive of Sf. Maria Hospital, Bucharest, Surgery Clinic 1, corresponding to the period January 1, 2019-31 December 2019.

In order to evaluate the contribution of esophageal manometry and 24-hour pH-metry in the diagnosis of reflux disease, 65 patients evaluated by these two investigations were selected with the purpose of establishing the final diagnosis. The inclusion criteria were the typical or atypical symptoms of reflux, the absence of esophagitis lesions on endoscopy and the lack of response to a treatment of at least 3 months with PPI in doses of maximum 80 mg/day.

The indication of pH-metry was given by doctors specialized in ENT, gastroenterology and surgery, considering both the definitive establishment of the diagnosis of reflux disease and possibly the indication of a surgical

strategy, the medical treatment being without effect.

For this purpose, consecutive patients were selected from the pH-metry software database over a period of time. We mention that all patients performed before pH-metry, a conventional esophageal manometry, with the establishment of lower esophageal sphincter (LES) parameters (mean pressure, abdominal length, total length) and esophageal body motility, assessed by amplitude and progression of contraction waves. One of the very important information obtained on manometry is the exact position of the LES in relation to the nostrils, making it possible to position the pH catheter, 5 cm above its upper limit.

Esophageal manometry was performed after a total fast of 6 hours minimum, patients having discontinued any medication that affects esophageal motility for at least 72 hours before the investigation. Esophageal manometry was performed using a low compliance electrohydraulic pump (Mui Scientific, Mississauga, Ontario, Canada) and an 8-channel liquid infusion catheter (Albyn Medical). The data were processed on a computer using the specialized program Phoenix V3, Albyn Medical Ltd. The amplitude, length and propagation of esophageal peristaltic waves and the total length, the length of the intra-abdominal segment and the mean pressure of the LES were studied. The catheter was passed transnasally and inserted until the tip with the 4 holes was in the stomach. The mean intragastric pressure was recorded, and then the catheter was retracted in steps of 0.5 cm until the tip reached the esophagus. The measurement of the LES parameters was then possible. After that, the catheter was withdrawn from the LES to the UES (upper esophageal sphincter, in steps of 1 cm, and esophageal body peristalsis was measured.

For the ambulatory pH metry, the patient had to discontinue any antisecretory medication for at least 10 days and any antacid for at least 3 days before the procedure. The procedure was performed after a total fast of at least 6 hours. After calibration of the device before the investigation, the pH-metry catheter, with the antimony tip, is inserted trans-nasally to the stomach, to check its correct position, without angles and the presence of an acid pH in the stomach. Once confirmed, the catheter was retracted and positioned 5 cm above the upper edge of the LES, determined manometrically, being fixed in position at the level of the nostril. The catheter is connected to a portable recording device, and the patient is instructed how to use it. The device has several buttons which records: the patient position, respectively ortho/clinostatism, when feeding or drinking fluids, and, most importantly, when he has symptoms. The investigation lasts 24 hours, during which time the patient is advised to behave as close to normal as possible, including not dieting. At the end of the investigation, based on the records made, the dedicated software returns the data in absolute format, but also integrates them into the DeMeester score.

Another important thing is to analyze the correlation between symptom and reflux. It has been found over time that this correlation is sometimes more important than the presence of pathological reflux. There are patients who have profound reflux, but the symptoms they complain of are not correlated with it and, perhaps even more frequently, patients with so-called esophageal hypersensitivity to reflux, in which, although in a normal amount for 24 hours (according to current standards), the symptoms are given by those smaller episodes of reflux.

From a therapeutic point of view, this information is even more important, because if the symptoms are not given by reflux, then after treatment, especially in the case of surgery, patients will not feel better and will have in addition the consequences of surgery, that sometimes becomes the source of all subsequent problems that the patient accuses.

However, to make sure that the pH-metry results and the reflux symptom correlation are not the result by chance, another parameter was created, namely Symptom Association Probability (SAP), which analyzes the results taking into account the total number of episodes per 24 hours. We also analyzed all the data to determine what percentage of patients who report typical and especially atypical symptoms of reflux, with negative endoscopy and lack of response to treatment, actually have reflux.

During the investigation, there were 14 patients who did not report any symptomatic

episodes. In these, the connection with esophageal reflux could not be evaluated. The data were subsequently introduced and interpreted in the SPSS statistical program, the variables being grouped according to two dimensions: patient identification data (such as age, sex, etc.) and data regarding the evaluation of esophageal reflux. The Fischer test was used to identify statistical significance (considered true if $p < 0.05$).

RESULTS AND DISCUSSION

Of the 65 patients included in the study, 54% were women aged between 20 and 74 years, 46% men, with a mean age of 52 years. Out of the total number of patients monitored on an outpatient basis for 24 hours, only 30% had acid reflux (defining acid reflux by a DeMeester score >14.7), without any particular gender distinction ($p=1$).

The most affected age group, for both sexes, was 51-60 years (45%), followed by 31-40 years (22%) (Figure 1).
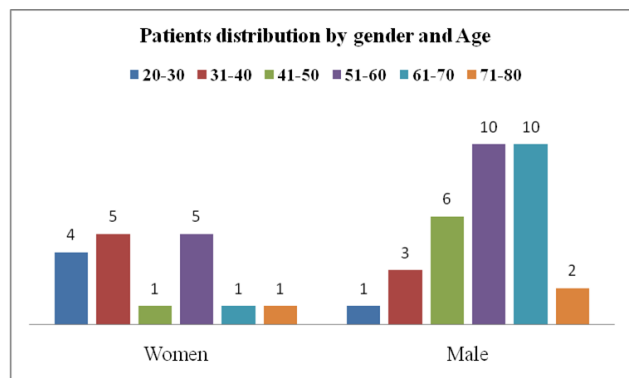

Figure 1 – Patients distribution by Gender and Age

80% of the patients included in the study had symptomatic episodes within 24 hours, ranging from a minimum of 1 episode to a maximum of 31 episodes. However, only 37% of these were identified in patients with an abnormal pH-metry result within 24 hours.

A percentage of 14% (n = 2 F and n = 1 B) of patients with pathological reflux did not show symptoms during the 24 hours, these representing a special category in the analyzed group. In these patients, the common element is the motility disorders in the context of a competent LES. In both females and males, esophageal manometry reveals concomitant

impairment of amplitude and peristalsis (Figure 2).
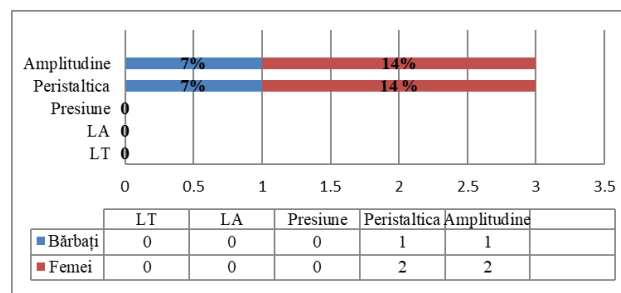
Figure 2 – Distribution of pathological changes in asymptomatic patients, with abnormal 24 hours ambulatory pH-metry

Statistical data suggest a higher frequency of symptomatic episodes in females, with women showing a total of 302 episodes related or not to acid reflux compared to 94 of males. In the analyzed group, there is a higher tendency in males for symptomatic events to be correlated with acid reflux (44%) compared to females in which only one association was found in 31% of cases.

The results of the pH-metry do not support the correlation between the duration of the reflux episode and the appearance of symptomatic episodes: at 7 patients the painful episodes appeared at a duration of the reflux episode less than 10 seconds, in 5 cases at a value between 11 and 20 seconds, at other 6 between 21-30, in one case the maximum duration of reflux was 120 seconds but was not manifest, and in other 3 situations the patients did not have reflux but associated symptomatic episodes. A number of 37 patients had a reflux duration of more than 5 minutes, in 22 of cases (59%) being correlated with a positive DeMeester score, with variations from 1 to 14 episodes longer than 5 min and with more than 10 symptomatic episodes (Figure 3).
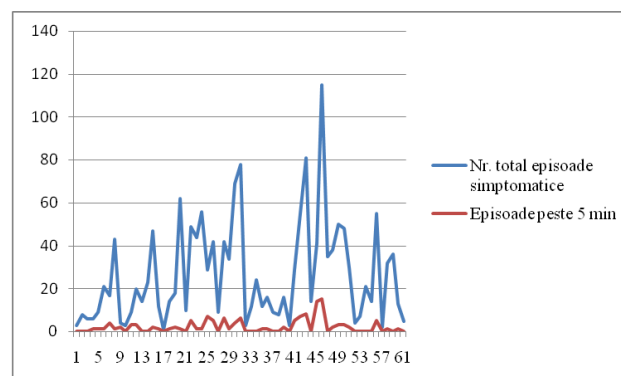
Figure 3 – Total number of symptomatic events vs reflux episodes longer than 5 min

The presence of pathological reflux depending on body position

In 59% of patients the reflux occurs in supine position, most of them presenting at the manometry the incompetence of the lower esophageal sphincter.

In 5% of cases the pathological reflux occurred in upright position, being influenced mostly by the number of reflux episodes (between 20 and 78). Researchers such as DeMeester [7], Joseph and Johnson explain the presence of reflux in orthostatism based on aerophagia or delayed gastric emptying. In another 18% of cases the reflux is manifested both in the supine and upright, being correlated with a higher frequency in females, over 50 years.

Those who have pathological reflux in both ortho- and clinostatism (n=7) have a longer duration of reflux, a higher number of symptomatic episodes (average of 382 episodes), of which 43% (n=3) recording changes in the total length of the lower esophageal sphincter and an abdominal length below 1.29% (n=2) are associated with pressure <6 mm/Hg, and 14% (n=1) have motility disorders and low blood pressure. Studies such as those of Fitzgerald [8], Ouatu-Lascar and Lin support the emergence of reflux in both positions as a prognostic marker of severe reflux disease.

Esophageal manometry

Specialist studies support the existence of three basic components that ensure a competent LES: abdominal length (> 1 cm), total length (> 2 cm) and pressure (> 10 mm / Hg). If one of these components is affected, the incidence of pathological acid reflux reaches 53%, increases to 74% when two are affected or 92% when all three are affected [9].

Our research data show that an abnormal 24-hour pH-metry result correlates in almost 60% of cases with a hypotonic or incompetent lower esophageal sphincter (Figure 4).

This statistical observation suggests that there are other mechanisms involved in the pathogenesis of reflux disease, even in the context of a competent LES. The identification of the pathological substrate of GERD is important as it guides, at a later stage, the treatment plan, patients with GERD and competent LES being, according to studies [10], the best responders of PPI therapy, not of antireflux surgery.
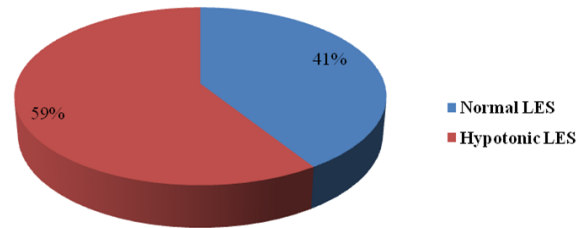
**Figure 4 – LES and Abnormal 24-Hour pH-metry**

In this sense, the data regarding the motility of the esophageal body were analyzed, respectively the amplitude and peristalsis, elements that define "the ability of the esophagus to produce the clearance of gastric reflux" [11]. Thus, 23% of patients with pathological reflux have changes in the amplitude of esophageal contraction waves, and in other 18% of cases the peristalsis is affected, which causes poor esophageal motility and a deficient acid clearance, exposing the esophageal mucosa to acid reflux (Figure 5).
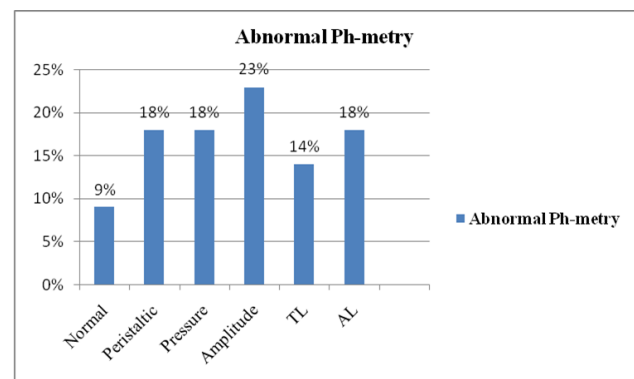
Figure 5 – Modified 24 hours pH-metry depending on the affected elements

Out of the total number of patients with esophageal motility dysfunctions, only a percentage of 39% has pathological reflux, in most cases (28% GERD - and 32% GERD +) the most affected being the amplitude of peristaltic waves. Our research supports some hypothesis [12] according to which the motility dysfunctions of the esophageal body have a

higher prevalence in patients with GERD, the amplitude being tempted to decrease with age, especially in the category 51-60. The increase of the rigidity of the esophageal walls [13], as a result of the aging process, as well as the damage of the neurons in the myenteric plexus, seem to play a defining role (Figure 6).
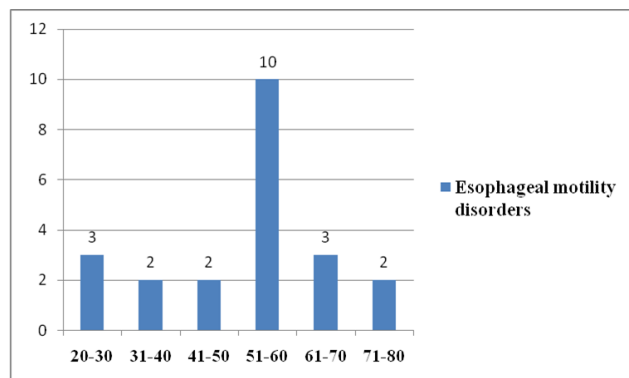
Figure 6 – Percentage of patients with esophageal motility disorders, GERD+, by age groups

Although the measurement of pathological acid reflux in the esophagus establishes the diagnosis of GERD, it is still not sufficient to determine whether the patient's symptoms are due to reflux. To identify this link, several indexes have been created:

SI (Symptom Index) - is an index of correlation between the onset of symptoms and the presence of pathological reflux. It is calculated by dividing the number of symptomatic episodes related to reflux by the total number of symptoms. If it is over 0.5, it is considered positive, the symptoms being most likely related to reflux. However, two other verification methods were created so that the results obtained were not the result of a random association.

SSI (Symptom Sensitivity Index) is defined as the number of symptomatic episodes related to reflux, divided by the total number of episodes of reflux x 100.

SAP (Symptom-Association Probability) is a simple statistical method of calculating the likelihood of symptoms being associated with reflux episodes.

During the investigation, the 65 patients experienced between 0 and 31 symptomatic episodes (the average being 10 episodes). A percentage of 22% of them did not show any symptoms in the 24 hours.

In 50% of patients the Symptom Index value is positive (SI>0.5), the lowest value recorded is 0 and the highest 100%, in 16% of cases (n=7) SI positive did not correlate with a pathological DeMeester score.

Regarding the distribution of Symptom Sensitivity Index in 37% of cases (n=24) it registered a positive value (SSI>10), the lowest value being 0 the highest 50, only in 12% of cases an SSI>10 being correlated with pathological reflux.

In 16 of the patients with confirmed reflux at pH-metry for 24 hours (n=22), the Fischer coefficient showed statistical significance being below the threshold value of 0.05 (p <0.05), the SAP value being over 96% in these cases.

In our study only one patient had an SI> 50 and SAP <95 (93%) the number of symptoms felt during the measurement and the SSI value being significantly lower (a single symptomatic episode). The smaller the number of symptomatic episodes, the more likely they are to be accidentally associated with acid reflux, as the low value of SAP proves this.

In patients with SI<50 and SAP>95, in one case the 24-hour pH-metry identified the pathological reflux. Also, in this patient, SSI recorded high values (11-40), which indicates that a significant percentage of reflux episodes are associated with symptoms, hence the SAP value is 95%. In the case of an SAP>95%, some studies [14] indicates that the probability of the observed association to occur randomly is less than 5%.

Studies concerning patients with symptoms and normal values at the esophageal pH monitoring are diverse. While some support the idea that a positive SI suggests a false negative test, others promote the concept of "visceral sensitivity."

In this sense, Fass and Dickman [15] are grouping the patients with reflux symptoms, but with negative results at pH-metry (the so-called "patients with functional pain"), in two categories according to the SI value: those with SI<50 (negative) in the category of "functional symptoms" and those with SI>50 (positive) in those with hypersensitivity to a physiological amount of acid, hence the name hypersensitive esophagus.

This category of patients [16] has been shown to have an abnormal perception of the painful threshold at balloon dilation, which demonstrates the involvement of "visceral hypersensitivity". They appear to have a more limited response to the standard dose of PPI, but with a marked improvement in symptoms at higher doses. Also, considering the solution of reflux pathology by surgical mechanisms, it should be mentioned that this type of patients is very unresponsive to antireflux interventions.

CONCLUSION

24-hour Ph-metry in our group showed that only one-third (30%) of patients with normal endoscopy and no response to medical treatment actually had reflux disease. Of the percentage of 70% of patients without changes in pH-metry for 24 hours who reported symptoms, 88% had a negative Symptom Index (SI<50%), most likely other factors being responsible for the symptoms' presence. The remaining 12% with a positive Symptom Index can be classified in patients with hypersensitive esophagus.

Both patients with abnormal pH metry and patients with hypersensitive esophagus may benefit from antireflux surgery as a therapeutic option.

REFERENCES

[1] Kahrilas P., GERD Pathigenesis. Pathophisiology and clinical manifestation in Cleveland Clinical Journal of Medicine, Vol.70 (5); 2003: S4-19.

[2] United European Gastroenterology, The Survey of Digestive Health Across Europe. Highlighting changing trends and healthcare inequalities in GI and liver disease, 2018.

[3] Chirila I., Morariu I., The Role of Diet in the overlap between gastroesophageal reflux disease and functional dyspepsia in Turk J Gastroenterol. 2016 Jan;27(1):73-80.

[4] OECD, România. Profilul Sănătăţii în 2017. State of Health in the UE. A se consulta online la (https://ec.europa.eu/health/sites/health/files/state/docs/chp_romania_english.pdf).

[5] CNAS, Top 10 medicamente eliberate prin farmaciile cu circuit deschis , pe baza de prescripţie medicală, în sistemul de asigurări sociale de sănătate în Trimestrul III, 2018. A se consulta online la (http://www.cnas.ro/media/pageFiles/TOP%2010%20DCI%20T3%202018%20CD.pdf).

[6] RASCI, Piaţa OTC în primul trimestru al 2018. A se consultaonline la: www.rasci.ro/datedesprepiata.

[7] Demeester TR, Johnson LF, Joseph GJ, Toscano MS, Hall AW, Skinner DB. Patterns of gastroesophageal reflux in health and disease. Ann Surg. 1976;184(4):459-470. doi:10.1097/00000658-197610000-00009

[8] Rodica Ouatu-Lascar, Otto S Lin, Rebecca C Fitzgerald, George Triadafilopoulos, Upright versus supine reflux in gastroesophageal reflux disease in Volume16, Issue11, November 2001, PP. 1184-1190

[9] Smith D., McClusky D., Esophagus. Benign Diseases of the Esophagus in Norton J., Barie P., Bollinger R, Chang A., Surgery. Basic Science and Clinical Evidence, Ed. Springer, 2008, pp. 807-808.

[10] Zaninotto G, DeMeester TR, Schwizer W, Johansson KE, Cheng SC. The lower esophageal sphincter in health and disease. Am J Surg. 1988;155(1):104-111. doi:10.1016/s0002-9610(88)80266-6

[11] Kahrilas P.J., Dodds W., Hogan W., Effect of Peristaltic Dysfunction on Esophageal volume clearance in Gastroenterol, 1988: 94:73-80.

[12] Martinucci I., De Bartoli N., Giacchino M., Savarino V., Savarino E., Esophageal motility abnormalities in gastroesophageal reflux disease in World J. Gastrointest. Pharmacol. Ther, 2014, mai 6, 5 (2); 86-96.

[1] Hori K., Kim Y., Sakurai J., et al. Non= Erosive reflux disease rather than cervical inlet patch involves globus in J. Gastroenterol, 2010, 45 (11): 1138-45.

[14] Weusten BL, Roelofs JM, Akkermans LM, Van Berge-Henegouwen GP, Smout AJ. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology. 1994;107(6):1741-1745.

[15] Fass R., Dickman R., Nonerosive reflux disease (NERD) - An Update. J Neurogastroenterol Motil. 2010; 16:8–21.

[16] Rodriguez-Stanley, Sheila, PhD1; Robinson, Malcolm, MD1; Earnest, David L, MD2; Greenwood-Van Meerveld, Beverley, PhD1; Miner, Philip B Jr., MD1 Esophageal Hypersensitivity May Be A Major Cause of Heartburn, American Journal of Gastroenterology: March 1999 - Volume 94 - Issue 3 - p 628-631