

# Different presentations of gastroesophageal reflux disease

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**Abstract.** Aim: The main objective of this study was to investigate whether erosive reflux disease (ERD), non-erosive reflux disease (NERD), and functional pyrosis (FP) are distinct diseases or components of the gastroesophageal reflux disease (GERD) spectrum. Methods: This was a prospective study. 88 patients in an outpatient, single study center, underwent upper endoscopy, esophageal manometry and 24-hr esophageal pH monitoring. The patients were classified after having upper endoscopy in two branches: with erosive reflux disease and non-erosive reflux disease. Esophageal manometry of the patients measured the amplitude pressure of the lower esophageal sphincter (LES). A mean pressure of less than 6 mm Hg was considered to be abnormal. For each group, contact of refluxed gastric acid with the esophageal mucosa (pH<4) and clearance parameters (number of reflux episodes) were evaluated. Results: Out of the 88 patients, 31 patients (35.22%) were found to have ERD, 9 (10.22%) were diagnosed with NERD, and 48 patients (54.54%) were found to have functional pyrosis (FP). Those with ERD were found to have an abnormal LES pressure (5.80±2.68 mm Hg), in contrast to those with NERD (7.55±5.52 mm Hg) and FP (14.41±7.57 mm Hg), who had normal LES pressure,  $p < 0.001$ . The acidic contact parameters were significantly higher and the clearance parameters were significantly lower, in those with ERD as compared to those with NERD and FP. The percent of total time the pH<4 was found to be statistically significantly higher in ERD (9.68± 6.21), as compared to NERD (6.38±1.66), and functional pyrosis (1.38±1.09),  $p < 0.001$ . In regard to the clearance parameters, the total number of reflux episodes (NRE) was statistically larger in ERD (77.01±47.82) group than those with NERD (59.22±39.30) and FP (16.9±17.54),  $p < 0.0001$ . Conclusion: Upper endoscopy, 24-pH monitoring, and esophageal manometry demonstrated that ERD, NERD, and FP are distinct phenotypical forms of GERD.

**Key Words:** gastroesophageal reflux disease, erosive reflux disease, nonerosive reflux disease, functional pyrosis, upper endoscopy.

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## Introduction

Gastroesophageal reflux disease (GERD), or the regurgitation of gastric acid into the esophagus, is the most common cause of upper gastrointestinal disorders (Katz & Gerson 2013; Chait 2010). It has a high prevalence worldwide, affecting between 10-20% in the Western world, and has a major impact on health-care cost (El-Serag et al. 2014; Gelaye et al. 2016). GERD is a widely used term, but it may encompass multiple diagnoses with variable degrees of severity and pathogenesis. By upper endoscopy GERD can have two forms of manifestation: endoscopically visible esophagitis and non-erosive reflux disease (NERD), when there is no visible inflammation (Guarner et al 2012; Matsumura et al 2017). The patients with reflux symptoms but no evidence of endoscopic esophagitis or abnormal acid reflux, are classified as having functional pyrosis (FP) according to ROME III Committee (Tamura et al 2015). Historically, erosive reflux disease (ERD), NERD, and FP have been assumed to be diseases on the overall GERD spectrum; however the retrospective studies which evaluated whether those with NERD progress to ERD, have shown conflicting results. (Savarino et al 2017). The aim of this study was to evaluate whether ERD, NERD and FP should be considered distinct diseases or whether they

are just different manifestations on the GERD spectrum. This question was addressed by analyzing the three groups endoscopically, pH-metrically and manometrically.

## Materials and methods

### Patient characteristics

Eighty-eight patients were enrolled in this study. These patients reported typical heartburn symptoms at least once a week for 6 months. They were investigated in the Digestive Endoscopy Laboratory of the 1st Medical Clinic, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Patients who had thorax, gastric, or esophageal surgery, or a history of primary or secondary motility disturbances (achalasia, scleroderma, diabetes mellitus, peripheral neuropathy, myopathies) were excluded.

Patients underwent an upper esophagogastroduodenoscopy (EGD), after which they were divided into ERD and NERD groups. Then, these patients underwent esophageal manometry. The lower esophageal sphincter pressures, as well as the peristaltic wave pressure, were measured in this procedure. Thereafter, they underwent 24-hr esophageal pH monitoring to quantify reflux contact and clearance parameters. These included

the percentage of total time when the pH <4, percentage of time when the pH <4 in the orthostatic and clinostatic position, the area under the curve when the pH <4 and the number of reflux episodes. Patients were asked to interrupt any anti-secretory, antacid, or prokinetic medication one week before the examination. This study was approved by the Ethical Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca and each patient signed the informed consent before to be enrolled.

### Upper endoscopy

To realize the upper endoscopy the patients were placed in the left lateral decubitus position and were sedated with midazolam, in dose of 3 – 5 mg, in accord with midazolam's monography. The endoscope (Olympus GIF Q145) was inserted into the mouth and passed along the esophagus. The distal part of the esophagus was carefully evaluated for the presence of injuries of the mucosa. Patients were divided into two groups, with erosive and non-erosive disease. For those with mucosal inflammation, the extent of the erosive esophagitis was classified according to Los Angeles esophagitis grading system. Grade A is defined as having mucosal breakdown no more than 5 mm that does not extend between the two folds. Grade B is mucosal breakdown that is more than 5 mm, not extending between two folds. Grade C is mucosal breakdown extending between two folds, but involving less than 75% of the mucosa, while grade D involves more than 75% of the mucosa (Lundell *et al* 1999). The presence or absence of a hiatal hernia (HH) was also determined by measuring the distance between the diaphragmatic hiatus and the Z line (gastroesophageal junction). If the distance was larger than 2 cm, the patient was considered to have HH.

### Esophageal manometry

Esophageal manometry measures intraluminal pressures and coordination of pressure activity of the muscles of the esophagus, and is used to diagnose motility disorders of the esophagus. This examination was performed by infusing water into a catheter with 8 canals linked to multiple encapsulated Baxter precision sensors. The information was transmitted and interpreted by the MEDA (Gadion, Cluj-Napoca) software. The manometry system was calibrated before every examination. The catheter was placed trans-nasally to the 55 cm level, with the first 4 openings placed at gastric level. The gastric pressure and the lower esophageal sphincter (LES) pressure were determined through two different techniques, rapid pull-through and steady pull-through. Rapid pull-through technique consisted of a rapid extraction of 10 cm/10 sec of a catheter from 50-40 cm, while identifying the maximum pressure at the LES level. The steady pull-through consisted of a slow retraction of 1 cm/30 sec. The distal and the proximal limit of LES was determined, as well as the LES pressure at the end-expiration.

The amplitude of the esophageal peristaltic waves was also determined with the catheter through the 4 sensors at the top of LES level, while the other 4 sensors were placed through the length of esophagus at 5 cm distance apart from one another. The patient was asked to take 10 swallows, each consisting of a 10 ml water bolus, and the amplitude of the esophageal peristaltic waves and their transmitted character were recorded. A mean of the amplitude of the esophageal peristaltic waves was recorded during the 10 swallow movements. Patients found

to have manometry modifications that were characteristic of a primary motor dysfunction were eliminated from the study. Recording the amplitude under 30 mmHg was considered as inefficient esophageal peristaltic wave.

### 24-h distal esophageal pH-monitoring

Patients were asked to discontinue any anti-secretory therapy, antacid or other medications that may modify the esophageal pH one week prior to the procedure. All subjects then underwent a 24-hour monitoring of the pH in the distal esophagus. A pH probe with a 2 mm caliber monocrystalline electrode (Sandhill) with internal reference and a manometric canal was inserted through the nostril into the stomach. The electrode was placed 5 cm above the LES in the distal esophagus, whose position was identified by esophageal manometry. Before and after each use, the electrode was calibrated in standard solutions of pH 1 and pH 7. The electrode was connected to a DXC 91 M multi-ion meter recording device, which recorded the values of the esophageal pH with a 4 second frequency for 24 hours. Acid reflux was defined as a decrease of esophageal pH < 4. The values, which were recorded in the internal memory of the device, were then downloaded on a computer and interpreted by the GastroPH.2 (Datronix, Cluj-Napoca). The following acidic contact parameters were determined: percent of time the pH <4, the percent of time the pH <4 in the clinostatic position, and the area under the curve when the pH <4. The following clearance parameters were also determined and include the total number of reflux episodes (NRE), the number of reflux episodes that were longer than 5 minutes, and the median duration of reflux episode (MDRE).

### Statistical analysis

Statistical Analysis was made using the SPSS 16.0 programs for Windows, Medcalc 10.3.0.0 (Demo Versions). To examine the differences between qualitative variables, the  $\chi^2$  test was used. The quantitative (continuous) variables were analyzed via the Kolmogorov-Smirnov test to determine if the normality condition is fulfilled. The differences between quantitative (continuous) variables were analyzed with the Student t-test (if the variables respected the normality condition), or Mann-Whitney U test (if this condition wasn't respected). The ANOVA test analyzed the mean of multiple groups. A  $p < 0.05$  value was considered statistically significant.

## Results

A total of 88 patients with heartburn were enrolled in this study. From these, 47 (53.40%) were women (mean age 43.4 years  $\pm 15.11$ ), and 41 (46.59%) were men (mean age 48.56 years  $\pm 13.39$ ). Of the general group, 31 patients (35.22%) were found to have erosive esophagitis and 57 (64.77%) were found to have non-erosive esophagitis. Of those with non-erosive disease, 9 patients (15.78%) were classified as having NERD and 48 (84.21%) were diagnosed with FP.

Of those with erosive esophagitis, 26 patients (83.87%) were classified in Los-Angeles class A or B and 5 (16.12%) were classified in Los-Angeles class C or D. There were no significant differences between the two sexes regarding the presence of certain esophagitis classes.

Table 1. Relationship between disease type and reflux parameters

		Mean	St. Dev.	p
%pH<4	FP	1.38	1.09	<0.001
	NERD	6.38	1.66	
	ERD	9.68	6.21	
Area pH<4	FP	0.59	0.57	<0.001
	NERD	3.1	1	
	ERD	5.16	4.02	
MDRE	FP	48.55	34.05	<0.001
	NERD	100.88	99.03	
	ERD	99.8	64.04	
%pH<4 in clinostatism	FP	0.68	1.18	<0.001
	NERD	5.08	3.56	
	ERD	10.51	8.34	
LES Pressure	FP	14.41	7.57	<0.001
	NERD	7.55	5.52	
	ERD	5.8	2.68	
Peristaltic wave pressure	FP	82.77	36.56	NS
	NERD	75.55	30.56	
	ERD	80.93	39.51	
NRE	FP	16.9	17.54	<0.001
	NERD	59.22	39.3	
	ERD	77.01	47.82	
NRE > 5 MIN	FP	0.14	0.41	<0.001
	NERD	2.11	1.05	
	ERD	4.64	4.38	
%pH>7.5	FP	7.99	13.04	NS
	NERD	12.02	17.6	
	ERD	4.63	8.28	

The acidic contact parameters varied among all three groups. The percent of total time the pH<4 was found to be statistically significantly higher in ERD (9.68± 6.21), as compared to NERD (6.38±1.66), and functional pyrosis (1.38±1.09), with a p<0.001 (Table 1). Also, the mean of the area under the curve with pH<4, was found to be statistically significantly higher in ERD (5.16±4.02), as compared to NERD (3.10±1.00), and functional pyrosis (0.59±0.57), with a p<0.001 (Table 1). The percent of time the when pH<4 in the clinostatism position is more than ten times higher is 10 fold higher than in ERD patients (10.51±8.34) as compared to FP (0.68±1.18), p < 0.001 (Table 1). In regards to the clearance parameters, the total number of reflux episodes and the number of reflux episodes over 5 minutes were statistically larger in ERD group than those with NERD and FP. Peristaltic wave pressure and the percent of time pH>7.5 was not statistically significant among the three groups. The total percent of time the pH <4 and the NRE are the most sensitive tests to determine erosive esophagitis (Table 2). The longer the esophagus is exposed to acid and the higher number of reflux episodes, the higher likelihood of developing erosive esophagitis.

Of the total 88 patients, 23 (26.13%) had hiatal hernias. Hiatal hernias were found in a higher portion of those with ERD. 17 patients of those with HH had ERD (73.91%), 2 patients (8.69%) had NERD and 4 (17.39%) had FP.

The LES pressure was calculated for all patients through manometry. A pressure below 6 mm Hg was considered abnormal and a pressure above 6 mm Hg was considered to be normal. The mean LES pressure in those with ERD was determined to be abnormal at 5.8 mm Hg (table 1). The mean LES pressure among those with NERD and FP were each above 6 mm Hg.

The relationship between LES pressure and HH was also analyzed. It was noted that of those with a hiatal hernia, 14 (60.86%) had an abnormal LES pressure, (p=0.002). The risk for a patient with an abnormal pressure value to have a hiatal hernia was 4.76 (CI 95% 1.73-13.07).

In this study 10 women and 21 men were diagnosed with ERD, 5 women and 4 men with NERD and 32 women and 16 men with FP. So, the absence of erosive esophagitis upon endoscopic examination has been recorded in a significantly higher proportion in women than men 37 vs 20 (78.72% vs 48.78%, p=0.007). Also, more females were diagnosed with FP as compared to males 32 vs 16 (68.08% vs 39.02%). Furthermore, it was noted that the female population had smaller values, regarding the contact parameters (the percent of time with pH <4, area under the curve with pH<4) and these values were statistically significant (table 3). Female patients also had stronger clearance parameters compared to males, in terms of LES pressure (12.34 vs 8.78 mm Hg, p=0.02), NRE (31.24 vs 55.2, p=0.01) (Table 4).

## Discussion

Historically, gastric acid has been implicated as the well-recognized component of reflux, responsible for creating symptoms of heartburn and producing lesions on the esophageal mucosa (Ma et al 2012). Recent studies have conflicting results about the extent of the acid reflux and its association in each of the diseases. Shapiro, et al performed a prospective study in which 121 patients with GERD underwent upper endoscopy and pH testing (Shapiro et al 2006). This study demonstrated that there was a similar extent of acid exposure among those with ERD and NERD, suggesting that factors other than acid reflux played a role in the development of esophagitis (Usai Satta & Oppia 2017). Other studies suggest that the amount of acid exposure is lined to the development of esophagitis, and that FP and NERD are on the spectrum of GERD and a precursor to ERD (Di Mario & Goni 2014) (Giacchino & Savarino 2013). This study attempts to calculate the extent of acid exposure among the different GERD groups and to determine whether the spectrum concept is accurate or if the GERD patient population should be considered three unique groups consisting of ERD, NERD, and FP. In an effort to answer this question, the three groups were analyzed via endoscopy, esophageal manometry, and 24-hr esophageal pH monitoring.

The acid exposure time (AET) can be defined by the reflux contact parameters, including the percent of time the pH<4, the area of the curve when the pH <4, and the nighttime acid exposure when the pH <4. The clearance parameters can be defined by the NRE, NRE>5 min, and mean duration of reflux episodes (MDRE). It was observed that the reflux contact and clearance exposures varied among the three groups. Those with ERD had a

Table 2. The sensitivity and specificity of pH-metric parameters to differentiate between patients with or without erosive esophagitis

	AUC	95% CI	Se (%)	Sp (%)	Cut off value
% pH<4	0.898	0.815-0.952	90.3	84.2	3.8
Area pH<4	0.87	0.78-0.93	87.1	74.1	1.2
MDRE	0.744	0.640-0.831	61.3	78.9	64
LES Pressure	0.847	0.755-0.915	83.9	75.4	8
Peristaltic wave pres.	0.512	0.404-0.621	67.7	42.1	75
%pH <4 in clinostatism	0.888	0.803-0.945	77.4	91.2	4
NRE	0.842	0.749-0.911	90.3	70.2	22
NRE > 5 min	0.853	0.761-0.919	83.9	75.4	0

Table 3. Comparison of reflux contact parameters and gender

	Area pH<4	% time with pH<4	% time with pH>7.5	%time recumbent pH<4
Male	3.42	6.7	7.2	6.64
Female	1.68	3.17	7.22	2.81
P	0.013	0.002	NS	0.008

Table 4. Comparison of reflux clearance parameters, manometry parameters and gender

	LES pres (mmHg)	Mean pres of peristaltic wave	NRE	NER>5min	MDRE (sec)
Male	8.78	8.78	55.2	3	84.87
Female	12.34	12.34	31.24	1	60.69
P	0.02	NS	0.01	0.005	0.056

statistically significant higher reflux exposure time and decreased reflux clearance parameters compared to those with NERD and FP. In addition, those with NERD have a higher reflux exposure and decreased clearance compared to those with FP. This study suggests that AET, NRE, MDRE are important factors in the pathogenesis of esophagitis induced by reflux. These results also emphasize the fact that not only the acidic reflux quantity, but also the clearance mechanisms of the esophagus, plays an important role in the production of erosive lesions. There is a statistically significant correlation between the severity of acid reflux and the grade of reflux esophagitis. Those with more reflux exposure have more severe grades of esophagitis.

According to recent studies, nonacid reflux can also be contributing to symptoms of heartburn (Storr 2011; Scarpellini et al 2016). In order to assess the effect of alkaline exposure on symptoms, its extent was calculated among the three groups. Alkaline exposure was considered to be abnormal if the pH was greater than 7.5 for more than 5% of the total examination time. The variation among the alkaline exposure was not statistically different among the three groups. Thus it was determined that non acid reflux was not responsible for the pathogenesis of mucosal lesion and that monitoring of non acid reflux monitoring brings little benefits for the differentiation of ERD, NERD, and FP.

This study further confirms the well-known association of hiatal hernias and ERD (Pointner 2017; Au Yeung & Cannon 2015). As observed in this study, a large majority (73.9%) of patients with ERD demonstrated a hiatal hernia on endoscopy. Hiatal hernias creates an abnormal LES, a weak barrier to the acid reflux, and thus predisposes those to erosive esophagitis (Torresan et al 2016; Hyun & Bak 2011).

There is a statistical association between LES hypotony and the different manifestations of GERD. The LES pressure was statistically lower in the ERD group, as compared to those with NERD and FP. The lower LES pressure, the more prone to reflux episodes (van Hoeij & Smout 2015).

In this study, esophageal motility was represented by distal esophageal peristaltic amplitude. There was no statistically significant difference among the three groups. The peristaltic wave amplitude had no diagnostic value. Thus, there does not appear to be a correlation between peristaltic wave pressure, which is a measure of acid clearance, and the development of esophagitis. A limitation of this study was that those found to have esophageal dysmotility were not further analyzed.

More females were diagnosed with non-erosive esophagitis (NERD and FP) as compared to males. These findings are consistent with other studies (Young Sun & Nayoung 2016; Lin et al 2004). Furthermore, there were significant gender differences regarding the esophageal reflux parameters. The female gender demonstrated lower reflux contact, as measured by the percent of time the pH <4, and the area under the curve with pH<4. Furthermore, women also had better defense mechanisms, as measured by the clearance parameters (LES pressure, NRE, NRE >5). With these significant differences, it can be postulated that women have a higher esophageal nociceptive sensitivity compared to men because although they had less contact parameters, they still report symptoms of regurgitation.

## Conclusion

The contact and clearance parameters statistically varied among the three groups. The mechanisms of GERD symptomatology are not only related to contact of acid reflux, but are also related to esophageal acid clearance, as well as presence of hiatal hernia, and an abnormal lower esophageal sphincter pressure. GERD has traditionally been viewed as a spectrum of diseases. Based on the findings in this study, it is evident that GERD should be divided into three individual diseases. This clarification is important because it has an impact on the mechanisms that lead to each disease and the treatment algorithm for each.

## References

- Au Yeung KJ, Cannon ML, Arkachaisri T, Gillespie S, Karnsakul W (2015) Impact of Hiatal Hernia on Pediatric Gastroesophageal Reflux Disease. *J Gastrointest Dig Sys* 5: 330.
- Chait MM. Gastroesophageal reflux disease: Important considerations for the older patients. *World J Gastrointest Endosc* 2010;2(12):388–96.
- El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2014;63(6):871–80.
- Gelaye B, Rondon M, Araya PR, A PM. Epidemiology of maternal depression, risk factors, and child outcomes in low-income and middle-income countries. *Lancet Psychiatry* 2016;3(10):973–82.
- Giacchino M, Savarino V, Savarino E. Distinction between patients with non-erosive reflux disease and functional heartburn. *Ann Gastroenterol* 2013;26(4):283–9.
- Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, et al. World Gastroenterology Organisation Global Guidelines. *J Clin Gastroenterol* 2012;46(6):468–81
- Hoeij FB, Smout AJ, Bredenoord AJ. Predictive value of routine esophageal high-resolution manometry for gastro-esophageal reflux disease. *J Neurogastroenterol Motil* 2015;27(7):963–70.
- Hyun JJ, Bak Y. Clinical Significance of Hiatal Hernia. *Gut Liver* 2011;5(3):267–77.
- Katz PO, Gerson LB, Vela MF. Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. *Am J Gastroenterol* 2013;108(3):308–28.
- Lin M, Gerson LB, Lascar R, Davila M, Triadafilopoulos G. Features of Gastroesophageal Reflux Disease in Women. *Am J Gastroenterol* 2004;99(8):1442–7.
- Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;45(2):172–80.
- Ma J, Altomare A, Guarino M, Cicala M, Rieder F, Fiocchi C, et al. HCl-induced and ATP-dependent upregulation of TRPV1 receptor expression and cytokine production by human esophageal epithelial cells. *Am J Physiol Gastrointest Liver Physiol* 2012;303(5):G635–45.
- Mario F, Francesco Di, Goni E. Gastric acid secretion: Changes during a century. *Best Pract Res Clin Gastroenterol* 2014;28(6):953–65.
- Matsumura T, Ishigami H, Fujie M, Taida T, Kasamatsu S, Okimoto K, et al. Endoscopic-Guided Measurement of Mucosal Admittance can Discriminate Gastroesophageal Reflux Disease from Functional Heartburn. *Clin Transl Gastroenterol* 2017;8(6):e94.
- Pointner R, [Gastroesophageal Reflux Disease (GERD) and Hiatal Hernia]. In: [Surgical Principles of Minimally Invasive Procedures] Cham: Springer International Publishing, pp. 47–51. Switzerland, 2017.
- Savarino E, Marabotto E, Bodini G, Pellegatta G, Coppo C, Giambro E, et al. Epidemiology and natural history of gastroesophageal reflux disease. *Minerva Gastroenterol Dietol* 2017;63(3):175–83.
- Scarpellini E, Ang D, Pauwels A, De Santis A, Vanuytsel T, Tack J. Management of refractory typical GERD symptoms. *Nat Rev Gastroenterol Hepatol* 2016;13(5):281–94.
- Shapiro M, Green C, Faybush EM, Esquivel RF, Fass R. The extent of oesophageal acid exposure overlap among the different gastro-oesophageal reflux disease groups. *Aliment Pharmacol Ther* 2006;23(2):321–9.
- Storr MA. What is nonacid reflux disease? *Can J Gastroenterol* 2011;25(1):35–8.
- Tamura Y, Funaki Y, Izawa S, Iida A, Yamaguchi Y, Adachi K, et al. Pathophysiology of functional heartburn based on Rome III criteria in Japanese patients. *World J Gastroenterol* 2015;21(16):5009–16.
- Torresan F, Mandolesi D, Ioannou A, Nicoletti S, Eusebi LH, Bazzoli F. A new mechanism of gastroesophageal reflux in hiatal hernia documented by high-resolution impedance manometry: A case report. *Ann Gastroenterol* 2016;29(4):548–50.
- Usai Satta P, Oppia F, Cabras F. Overview of pathophysiological features of GERD. *Minerva Gastroenterol Dietol* 2017;63(3):184–97.
- Young Sun K, Nayoung K, Gwang Ha K. Sex and gender differences in gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2016;22(4):575–88.

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**Citation** Cătinean A, Neag MA, Pop D. Different presentations of gastroesophageal reflux disease. *HVM Bioflux* 2017;9(4):111-115.

**Editor** Ștefan C. Vesa

**Received** 1 September 2017

**Accepted** 2 October 2017

**Published Online** 7 October 2017

**Funding** None reported

**Conflicts/  
Competing  
Interests** None reported