Acta Biomed 2018; Vol. 89, Supplement 8: 33-39 DOI: 10.23750/abm.v89i8-S.7963

Review

Diagnosis of GERD in typical and atypical manifestations

Silvia Cesario[1], Serena Scida[1], Chiara Miraglia[1], Alberto Barchi[1], Antonio Nouvenne[1], Gioacchino Leandro[2], Tiziana Meschi[1], Gian Luigi de' Angelis[1], Francesco Di Mario[1]

[1] Department of Medicine and Surgery, University of Parma, Parma, Italy; [2] National Institute of Gastroenterology "S. De Bellis" Research Hospital, Castellana Grotte, Italy

Summary. The manifestations of gastroesophageal reflux disease (GERD) have been recently classified into either esophageal or extra-esophageal syndromes. Clinical history, questionnaire data and response to antisecretory therapy are insufficient to make a conclusive diagnosis of GERD. Endoscopy had a low sensitivity. Recently, the availability of multichannel intraluminal impedance and pH-monitoring (MII-pH) has modified the diagnostic approach towards atypical manifestations of GERD. There is a rising consensus that this technique should be considered as the gold standard for GERD diagnosis. Gastrin 17 (G-17) has been proposed as a non-invasive marker of GERD, due to the negative feedback between acid and the hormone. G17 levels seem able to identify patients with acid and non-acid reflux. (www.actabiomedica.it)

Key words: GERD, diagnosis, typical manifestations, atypical manifestations, pH impedance, gastrin 17

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders in Western countries (1). The clinical features of GERD have been recently classified into either esophageal or extra-esophageal syndromes (2). Most common atypical manifestation of GERD may include ear, nose, and throat (ENT), pulmonary (chronic cough or asthma), or cardiac (noncardiac chest pain) symptoms (3). Therefore, GERD should be strongly considered in the differential diagnosis of patients presenting with atypical symptoms when alternative diagnoses have been excluded by other specialist (ENT surgeons, cardiologists, pneumologists, allergists).

The diagnosis of GERD is very difficult and is typically made by a combination of clinical symptoms, response to acid suppression, as well as objective testing with upper endoscopy and esophageal pH monitoring.

Empirical therapy

In patients with a history suggestive of uncomplicated GERD manifesting in typical symptom of heartburn and/or regurgitation can be offered empiric treatment (4). Typical symptoms that are responsive to acid suppression offer additional evidence for pathologic esophageal acid exposure and it's reasonable to assume a diagnosis of GERD in patients who respond to appropriate therapy. On the other hand, typical symptoms that do not improve warrant further tests to demonstrate the existence of GERD and evaluate for an alternate diagnosis. Similarly, patients with atypical manifestations or non-cardiac chest pain should be considered for esophageal function tests prior to empiric therapy (5).

However, this empirical test is contraindicated in patients with alarm symptoms such as dysphagia, weight loss and bleeding in according to the five recommendations of the Italian Association of Hospital Gastroenterologist (AIGO).

Upper endoscopy

Upper endoscopy allows to evaluate the esophageal mucosa in patients with GERD and obtains biopsies of concerning lesions (e.g. Barrett's metaplasia, strictures or masses). There are limitations with the use of upper endoscopy in the diagnosis of GERD. Erosive reflux disease (ERD) occurs in a minority of patients with GERD (<30%), whereas the majority of them are included in the non-erosive reflux disease (NERD) phenotype, characterized by typical reflux symptoms, mainly heartburn, without any esophageal mucosal lesion visible on upper endoscopy (6). Patients with atypical GERD symptoms usually have a low prevalence of endoscopic esophagitis (3). Therefore, an upper endoscopy is not required for the diagnosis and is mostly performed for evaluation of GERD associated complications and alternative diagnoses. Patients with alarm symptoms, such as anemia, weight loss and dysphagia, or history of chronic GERD and age 50 years or older should receive screening endoscopy for Barrett's esophagus (7,8).

Barium radiographs

Barium radiographs have been historically considered part of the potential diagnostic armamentarium in the patient with esophageal symptoms, including GERD. Although well-performed barium esophagrams with double contrast can detect signs of esophagitis, the overall sensitivity of this test is extremely low (9). The finding of barium reflux above the thoracic inlet with or without provocative maneuvers including the water siphon test does increase the sensitivity of the barium test; however, not sufficiently to be recommended as a diagnostic test without dysphagia (10).

Esophageal manometry

Esophageal manometry is currently considered the gold standard test for the diagnosis of esophageal dysmotility that may be responsible for symptoms like dysphagia and chest pain. However, it has shown limited capability in diagnosing GERD. With the advent of high-resolution manometry (HRM), more accurate evaluations of esophageal motility are now possible. Furthermore, new metrics have been developed to investigate esophagogastric junction (EGJ) morphology and function. In particular, the anti-reflux barrier function of EGJ can now be assessed evaluating the contraction integral of the junction. Also, transient lower esophageal relaxations can be defined more precisely with HRM. Neither a decreased lower esophageal sphincter pressure, nor the presence of a motility abnormality is specific enough to make a diagnosis of GERD. Manometry should be used to aid in placement of transnasal pH-impedance probes and is recommended before consideration of anti-reflux surgery primarily to rule out achalasia or severe hypomotility (scleroderma-like esophagus), conditions that would be contraindications to Nissen fundoplication, but not to tailor the operation (11).

24 hours bilimetry

Bilimetry allows spectrophotometric measurements of esophageal luminal bilirubin concentration due to duodenogastric reflux (DRGE).

Although the role of bile in the pathogenesis of esophageal mucosal damage is unknow and there is a high prevalence of both acid and non-acid refluxes, some Authors recommend simultaneous pH monitoring and bilimetry (12, 13).

The main indications for double monitoring are patients with typical GERD symptoms poorly responsive to PPI therapy.

Bilitec 2000 is a new spectrophotometric system. Unfortunately, this technology is only a semiquantitative measure for detecting DRGE. Validation studies found that this instrument underestimates bile reflux in an acid medium (pH < 3.5) (14). In solutions with pH < 3.5, bilirubin undergoes a monomer to dimer isomerization which is reflected by the shift in the absoption wavelength from 435 nm to 400 nm. Because Bilitec readings are based on the detection of absorption at 470 nm, this shift underestimates the degree of DRGE. Therefore, Bilitec measurements of DRGE must always be accompanied by the simultane-

ous measurements of acid exposure by pH monitoring. Furthermore, a variety of substances can cause false positive readings by the Bilitec, because it indiscriminately records any substance absorbing around 470 nm such as heme (i.e. during hematemesis), porphyrin, carotenoids, riboflavin and various foods such as tomatoes, bananas, carrots, beets, parmesan, cheese, meat, tea and coffee (15). In addition, solid food can obstruct the tip of the probe and reduce the accuracy of the recordings, for these reasons standardized liquid diets should prescribe to allow registrations. However, there is a limitation in the registration of DRGE patterns due to a different and a lower caloric content diet.

Despite the measurement of bilirubin adds valuable information on the chemical nature of the flowed material, there are several limitations that do not allow to accurately and accurately detect the onset and frequency of episodes of DGER.

Table 1. DeMeester score

Percent total time pH < 4
Percent Upright time pH < 4
Percent Supine time pH < 4
Number of reflux episodes
Number of reflux episodes ≥ 5 min
Longest reflux episode (minutes)

Ambulatory pH monitoring

Ambulatory reflux monitoring is the only modality allowing direct measurement of esophageal acid exposure (acid exposure time, AET), reflux episode frequency and association between symptoms and reflux episodes. It's typically used to evaluate patients without endoscopic evidence of GERD, in order to confirm the diagnosis. It can also be employed to monitor the control of reflux in those on therapy with persistent symptoms.

24 h pH-metry allows to monitor the presence of acid in esophagus recorded over 24 hours by means of a transnasal pH catheter positioned near the lower esophagus. When there is a the passage of acid gastric contents into the esophagus during the reflux it causes a decrease in the esophageal pH. The test is considered positive if the pH falls below 4 for a period longer than 5 seconds. A patient's tracing is analyzed, and the results are expressed using six standard components. Of these 6 parameters a pH score called DeMeester Score has been calculated, which is a global measure of esophageal acid exposure (Tab. 1) (16). A DeMeester score > 14.72 indicated reflux.

There are limitations with the use of 24 h-pH metry for the diagnosis of GERD. The frequency of symptoms it's variable. It's unlikely that symptoms will occur during a routine 24-hour monitoring session and therefore a single measurement may not be representative. Also, the pH monitoring cannot diagnose non-acid reflux (pH> 4) (17).

24 h esophageal pH-impedance monitoring is a technique used in the diagnosis of GERD, by monitoring both impedance and pH. An impedance pH probe is inserted into the nostril and advanced into the esophagus. The impedance pH probe will remain in place for 24 hours and is connected to a small recorder.

Impedance measurement permits the detection of anterograde and retrograde bolus (liquid, gas or mixed) flow in the esophagus and combined-pH monitoring allows the chemical characterization of the refluxate. pH-impedance monitoring can detect not only acid (pH < 4) but also weakly acid (4 < pH < 7) and non-acid (pH > 7) gastric contents. This increases the diagnostic yield of reflux monitoring in patients with GERD (18).

After completion of the impedance-pH study, data are analyzed using appropriate software and interpreted by the reporting physician. The software identifies individual reflux and swallow events, measures symptom-reflux association and distinguishes changes in impedance that are not clinically important. Automated analysis is adequate for acid reflux events but overestimates non-acid or weakly acid events. As consequence calculation of Symptom Index (SI) and Symptom Association Probability (SAP) might be affected. A manual review of the 2 minutes preceding each symptom event in pH-impedance studies is recommended (19).

Acid exposure time (AET) was calculated as the percentage of time the pH was less than 4 at the distal esophageal pH sensor. The Lyon Consensus proposes that AET < 4% be considered definitively normal (physiological) and > 6% be considered definitively abnormal. Intermediate values identify a "grey area" in which additional evidence from other tests may provide the presence of pathologic acid burden (19, 20). Furthermore, there is a considerable day-to-day variability in AET measurements so a clinical decision should never be made exclusively based on this parameter (21).

Some Authors have evaluated a correlation between numbers of reflux episodes and GERD. A clearly high number of reflux episodes (above 80) might be considered abnormal while a number of reflux episodes on pH-impedance of 40 or few are considered ad normal. However, number of reflux episodes alone is not predictive of treatment outcome but an adjunctive tool (19, 20).

Symptom reporting during ambulatory 24-hours reflux monitoring allows investigation of the temporal relationship between reflux and symptom. The pH-impedance allows to modify the diagnostic analysis for atypical GERD manifestations such as cough, asthma, laryngitis and non-cardiac chest pain (22-25). Only symptoms that can reasonably be related to reflux episodes such as cough, chest pain, heartburn, and regurgitation are considered for symptom reflux association analysis. It's not possible to perform reliable symptom reflux association analysis for symptoms that lack a crisp onset and are chronically present, such as dyspnea or hoarseness (26).

The relationship between symptomatic events and reflux episodes can be evaluated with SI and SAP. The SI is defined as the percentage of symptom events that are related to reflux episodes, thus number of reflux related symptomatic events divided by total number of symptomatic events times 100%. The most often used cut-off is 50%, which means that above 50% the SI is considered positive (27). There is not necessarily a correspondence between SI and the acid exposure in the esophagus. The major defect of SI is that it doesn't considered the total number of reflux episodes; as consequence, the probability that SI becomes positive increases with the increase in the number of reflux episodes. The SI presents another limit: this index doesn't integrate all the factor that determine the relationship between symptoms and reflux.

The SAP is a statistical parameter that express the strength of the relationship between symptom events and reflux episodes during measurement. The calculation is more complex than the SI and cannot be done manually but it calculated instead by the measurement software. The cut-off for the SAP is 95%, and a SAP above 95% (corresponding to $P<0.05$, applying Fisher's exact rest on a 2x2 table) is considered positive for a relationship between symptomatic events and reflux episodes (28).

These indices have some limitations, especially related to day-to-day variability of reflux burden and occurrence of symptomatic events during the monitoring day. The presence of positive SI and positive SAP together provides the best evidence of a clinically relevant association between reflux events and symptoms. If one test is positive and the other is negative, this represents a grey area and further interpretation with other parameters and clinical factors are necessary (19).

Non erosive reflux disease (NERD) represents the more common phenotypic presentation of GERD and these patients are markedly heterogeneous from a pathophysiological point of view and should be (correctly?) by means of 24 h impedance-pH monitoring. This technique is able to identify three subsects of NERD, so called "NERD umbrella" (29):

1. Patients with "true" NERD characterized by pathological AET;
2. Patients with Hypersensitive Esophagus (HE) characterized by normal AET and positive SI/SAP for acid or weakly acid reflux;
3. Patients with Functional Heartburn (FH) who do not have any kind of reflux underlying their symptoms and must be excluded from the realm of GERD.

According to Roma III, FH is not a GERD subcategory and it's classified as functional disorder (30). Patients of group 1 and 2 need to be treated with reflux inhibitor. Patients with functional heartburn shouldn't undergo therapy with PPI (31).

Recent studies showed the added diagnostic value of two new pH-impedance parameters, post reflux swallow-induced peristaltic wave (PSPW) index and mean nocturnal baseline impedance (MNBI).

Chemical clearance consists of a salivary swallow, elicited by a post-reflux esophago-salivary vagal reflex and delivering salivary bicarbonate and epidermal growth factor to the esophagus, this augments pH and hastening repair of mucosal damage. A PSPW was define as an antegrade 50% drop in impedance occurring within 30 s of a reflux event, originating in the most proximal impedance channel, reaching the most distal impedance sites, and followed by at least 50% return to the baseline. An index of chemical clearance, namely PSPW index, was obtained by dividing the number of PSPWs by the number of total reflux events.

Baseline impedance values reflect the permeability of the esophageal mucosa. Low baseline esophageal mucosal impedance has been linked to alteration in intercellular space and tight junction and to the reflux symptoms. MNBI was assessed form the most distal impedance channel during the nighttime recumbent period. Three 10-minute time periods (around 1.00 am, 2.00 am and 3.00 am) were selected, excluding swallows, refluxes and pH drops; and the mean of the three measurements was calculated to obtain the MNBI.

Previously established cut-off values for PSPW index and MNBI were 61% and 2292 R respectively (Fig 1). The PSPW index and MNBI increase the

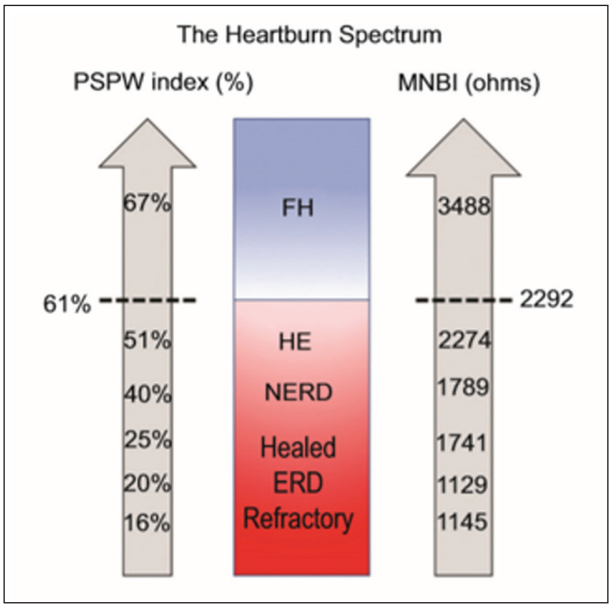

Figure 1. Median values of PSPW index and MNBI for the various diagnostic categories in the heartburn spectrum

diagnostic yield of impedance-pH monitoring in GERD patients as compared with healthy control. The PSPW index has lower values in ERD than in NERD patients and in both groups as compared with no-GERD subjects (32). MNBI distinguishes PPI-responsive from PPI-refractory heartburn patients with normal conventional impedance-pH variables and associated with greater probability of PPI response in patients with chronic cough. In clinical practice these novel impedance-detected parameters can distinguish reflux-related from reflux-unrelated heartburn in patients with normal AET. The very high sensitivity of both parameters allows excluding reflux disease when normal values are found.

PSPW index and MNBI have also a diagnostic value in patients on-therapy evaluated by impedance-pH monitoring. PSPW index and MNBI efficiently distinguish PPI-refractory NERD from FH.

Low MNBI (< 2292 R) independently predicts response to anti-reflux therapy. Frazzoni et al. hypothesize that abnormal PSPW index represents an independent predictor of PPI-refractory GERD, possibly due to a defective esophago-salivary vagal unaffected by surgical treatment. It is conceivable that persistent impairment of chemical clearance is rendered clinically latent after successful surgery owing to sub-total abolition of reflux events, which in turn determines restoration of mucosal integrity, as indicated by improved MNBI and then persistent heartburn remission (33).

Gastrin 17

Gastrin 17 (G-17) is a gastrointestinal peptide hormone and is involved in the control of gastric acid secretion. It's secreted almost exclusively by antral G cells. G-17 controls gastric acid secretion with a negative feedback mechanism. G cells are stimulated by high intragastric pH. High acidity in the stomach inhibits the secretion of G-17. So gastrin levels reflect indirectly intragastric acidity (Fig. 2) (34).

Sipponen et al. have evaluated that the serum levels of G-17 were lower in patients with Barrett's esophagus (BE) than in non-BE controls (34).

Franceschi et al. assessed the role of Gastropanel® (Biohit Oji, Finland), a non-invasive serological test,

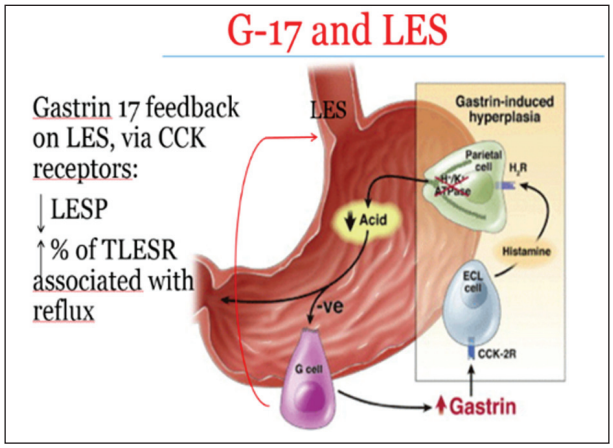

Figure 2. Role of G-17 in the control of gastric acid secretion

for the screening of chronic atrophic gastritis in a dyspeptic population. In this population people with GERD showed significant lower level of G-17 than other group of patients (35). Goni et al. confirmed that results and established that G-17 value < 1,9 pmol/L are useful for the diagnosis of GERD (36).

The role of G-17 in the diagnosis of GERD was assessed by pH-metry and pH-impedance in two different study. In both studies it was possible to conclude that the G-17 seemed to be able to identify patients with GERD and assess the nature of reflux (37, 38).

Low levels of G-17 are useful to identifying not only patients with typical symptoms but also those with atypical manifestations of GERD (39).

Therefore, he serum level of G-17 is proposed as promising and useful first level examination for the diagnosis of GERD even in atypical manifestations.

GastroPanel® Gastrin-17 is an enzyme-linked immunosorbent assay (ELISA) for the quantitative measurement of gastrin-17 (G-17) in human EDTA plasma samples.

Conclusions

GERD is a complex disease with heterogeneous symptoms and a multifaceted pathogenic basis that defies a simple diagnostic algorithm or categorical classification.

Ambulatory pH monitoring of the esophagus helps to confirm gastroesophageal reflux in patients with persistent symptoms (both typical and atypical) in the absence of esophageal mucosal damage, especially when a trial of acid suppression has failed.

The novel metrics from pH-impedance monitoring, MNBI and PSPW index, can distinguish GERD from No-GERD patients and predict PPI response.

Future studies are warranted to confirm the value of Gastrin-17 as non-invasive marker for GERD diagnosis, both in patients with typical and atypical symptoms.

References

1. El-Serag, Hashem B., et al. "Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review." Gut (2013): gutjnl-2012.
2. Vakil, Nimish, et al. "The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus." The American journal of gastroenterology 101.8 (2006): 1900.
3. Vaezi, Michael F. "Atypical manifestations of gastroesophageal reflux disease." Medscape General Medicine 7.4 (2005): 25.
4. Lacy, Brian E., et al. "The diagnosis of gastroesophageal reflux disease." The American journal of medicine 123.7 (2010): 583-592.
5. Aanen, M. C., et al. "Diagnostic value of the proton pump inhibitor test for gastro-oesophageal reflux disease in primary care." Alimentary pharmacology & therapeutics 24.9 (2006): 13771384.
6. Savarino, Edoardo, et al. "Drugs for improving esophageal mucosa defense: where are we now and where are we going?." Annals of gastroenterology 30.6 (2017): 585.
7. Shaheen, Nicholas J., Dawn Provenzale, and Robert S. Sandler. "Upper endoscopy as a screening and surveillance tool in esophageal adenocarcinoma: a review of the evidence." The American journal of gastroenterology 97.6 (2002): 1319.
8. Emami, Mohammad Hasan, Masoud Ataie-Khorasgani, and Nasim Jafari-Pozve. "Diagnostic value of alarm symptoms for upper GI malignancy in patients referred to GI clinic: A 7 years cross sectional study." Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences 22 (2017).
9. Johnston, Brian T., et al. "Comparison of barium radiology with esophageal pH monitoring in the diagnosis of gastroesophageal reflux disease." American Journal of Gastroenterology 91.6 (1996).
10. Katz, Philip O., Lauren B. Gerson, and Marcelo F. Vela. "Guidelines for the diagnosis and management of gastroesophageal reflux disease." The American journal of gastroenterology 108.3 (2013): 308.
11. Savarino, Edoardo, et al. "Practice guidelines on the use of esophageal manometry–A GISMADSIGE-AIGO medi-

cal position statement." Digestive and Liver Disease 48.10 (2016): 1124-1135.
12. Tack, Jan, et al. "Gastroesophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's esophagus: acid reflux, bile reflux, or both?." The American journal of gastroenterology 99.6 (2004): 981.
13. Stein, H. J., et al. "Bile reflux in benign and malignant Barrett's esophagus: effect of medical acid suppression and Nissen fundoplication." Journal of Gastrointestinal Surgery 2.4 (1998): 333-341.
14. Vaezi, Michael F., Richard G. Lacamera, And Joel E. Richter. "Validation studies of Bilitec 2000: an ambulatory duodenogastric reflux monitoring system." American Journal of Physiology-Gastrointestinal and Liver Physiology 267.6 (1994): G1050-G1057.
15. Tack, Jan, et al. "Dietary restrictions during ambulatory monitoring of duodenogastroesophageal reflux." Digestive diseases and sciences 48.7 (2003): 1213-1220.
16. Johnson, Lawrence F., and Tom R. DeMeester. "Development of the 24-hour intraesophageal pH monitoring composite scoring system." Journal of clinical gastroenterology 8 (1986): 52-58.
17. Vaesi, Michael F., Patrick L. Schroeder, and Joel E. Richter. "Reproducibility of proximal probe pH parameters in 24-hour ambulatory esophageal pH monitoring." American Journal of Gastroenterology 92.5 (1997).
18. Sifrim, Daniel, and F. Fornari. "Esophageal impedance–pH monitoring." Digestive and Liver Disease 40.3 (2008): 161-166.
19. Roman, S., et al. "Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group." Neurogastroenterology & Motility 29.10 (2017): 1-15.
20. Gyawali, C. Prakash, et al. "Modern diagnosis of GERD: the Lyon Consensus." Gut (2018): gutjnl-2017.
21. Zerbib, F., et al. "Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian–French cohort of healthy subjects." Alimentary pharmacology & therapeutics 22.10 (2005): 1011-1021.
22. Pauwels, Ans, et al. "Cough and gastroesophageal reflux: from the gastroenterologist end." Pulmonary pharmacology & therapeutics 22.2 (2009): 135-138. 127.
23. Savarino, Edoardo, et al. "Gastroesophageal reflux and pulmonary fibrosis in scleroderma: a study using pH-impedance monitoring." American journal of respiratory and critical care medicine 179.5 (2009): 408-413. 128.
24. Bigatao, Amilcar M., et al. "Chronic Obstructive Pulmonary Disease Exacerbations Are Influenced by Gastroesophageal Reflux Disease." The American Surgeon 84.1 (2018): 51-55. 129.
25. Prakash, Chandra, and Ray E. Clouse. "Wireless pH monitoring in patients with non-cardiac chest pain." The American journal of gastroenterology 101.3 (2006): 446.
26. Abdul-Hussein, Mustafa, Crystal Zhang, and Donald Castell. "Symptom Index or Symptom Association Probability?." Journal of clinical gastroenterology 52.1 (2018): e7-e10.
27. Wiener, G. J., et al. "The symptom index: a clinically important parameter of ambulatory 24hour esophageal pH monitoring." American Journal of Gastroenterology 83.4 (1988).
28. Weusten, Bas LAM, et al. "The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data." Gastroenterology 107.6 (1994): 1741-1745.
29. Savarino, Edoardo, Patrizia Zentilin, and Vincenzo Savarino. "NERD: an umbrella term including heterogeneous subpopulations." Nature Reviews Gastroenterology & Hepatology 10.6 (2013): 371
30. Savarino, Edoardo, et al. "The added value of impedance-pH monitoring to Rome III criteria in distinguishing functional heartburn from non-erosive reflux disease." Digestive and Liver Disease 43.7 (2011): 542-547.
31. Savarino, Vincenzo, et al. "Functional heartburn and non-erosive reflux disease." Digestive diseases 25.3 (2007): 172-17
32. Frazzoni, L., et al. "Postreflux swallow-induced peristaltic wave index and nocturnal baseline impedance can link PPI-responsive heartburn to reflux better than acid exposure time." Neurogastroenterology & Motility 29.11 (2017): e13116.
33. Frazzoni, M., et al. "The added diagnostic value of postreflux swallow-induced peristaltic wave index and nocturnal baseline impedance in refractory reflux disease studied with on-therapy impedance-pH monitoring." Neurogastroenterology & Motility 29.3 (2017): e12947.
34. Sipponen, Pentti, et al. "Low circulating levels of gastrin-17 in patients with Barrett's esophagus." World Journal of Gastroenterology: WJG 11.38 (2005): 5988.
35. Franceschi, Marilisa, et al. "Sa1749 Serological Diagnosis of Upper GI Diseases in Primary Care Setting." Gastroenterology148.4 (2015): S-322.
36. Goni, Elisabetta, et al. "Mo1135 Gastrin 17 As Non Invasive Marker of Reflux Disease." Gastroenterology 148.4 (2015): S-616.
37. Landi, S., et al. "P. 01.13: Gastrin-17 as a Non-Invasive Marker for Gerd: A Prospective Study on Sample of 777 Consecutive Patients." Digestive and Liver Disease 49 (2017): e137.
38. Savarino, Edoardo V., et al. "Gastrin 17 in Singling Out Patients with Different Patterns of Refluxate: A Pilot Study Using Impedance-pH as Reference Standard." Gastroenterology 152.5 (2017): S653.
39. de Bortoli, N., et al. "P. 06.20 Gerd diagnosis in 340 patients with atypical or extra-esophageal symptoms by using a non invasive surrogate test." Digestive and Liver Disease 50.2 (2018): e187.

Correspondence:
Silvia Cesario
Department of Medicine and Surgery,
University of Parma, Parma, Italy
E-mail: silvia.cesario@studenti.unipr.it