Diagnostic Investigations of Gastroesophageal Reflux Disease: Who and When to Refer and for What Test?

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Summary

Background: Due to the high prevalence and incidence of patients with gastroesophageal reflux disease (GERD), the diagnostic workup of patients with symptoms of GERD needs to be balanced between empiric antisecretory therapy and further functional assessment including endoscopy and reflux monitoring. **Methods:** This article is based on a literature review (PubMed, Medline) using the terms ‘gastroesophageal reflux disease’ or ‘GERD’ and ‘diagnosis’, ‘therapy’, or ‘PPI’ with special and critical analysis of the current ‘Porto’ consensus report. **Results and Conclusions:** Further diagnostics are mandatory in case of alarm symptoms as well as atypical or persistent symptoms under adequate therapy with proton pump inhibitors (PPI). In general, the clinical situation needs to be clarified before sending the patients for reflux monitoring. The question is not only when and whom to test but also how to test: *on* or *off* PPI therapy, pH-metry, or combined pH-impedance analysis. These questions have been defined in a recent consensus report of an international panel of experts and are further discussed in this article.

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Introduction

Gastroesophageal reflux disease (GERD) is one of the most common diseases in developed Western world countries. Up to 20% of the US population suffer from weekly symptoms, and even up to 40% report about intermittent symptoms [1, 2].

It is evident that GERD is caused by gastric contents exposed to the distal esophagus, causing troublesome symptoms and/or mucosal lesions [3]. The severity of symptoms is independent from the presence or severity of mucosal lesions [4, 5]. All patients, notwithstanding if they present with erosive reflux disease (ERD) or with normal appearing gastroesophageal junction (non-erosive reflux disease (NERD)), show distinct changes of the mucosa, such as molecular and microscopic signs of inflammation [6, 7].

In the presence of heartburn and regurgitation, clinical guidelines recommend GERD to be diagnosed as a symptomatic disease and to start antisecretory treatment with proton pump inhibitors (PPI) [8, 9]. Regarding the amount of patients, this is also a pragmatic way of disease management and to prevent an overload of healthcare systems. In the presence of alarm symptoms (dysphagia, anemia, bleeding, weight loss) and atypical symptoms (chest pain, laryngopharyngeal symptoms), upper endoscopy is mandatory (esophagogastroduodenoscopy (EGD)) [10, 11].

In case of persisting symptoms, exclusion of esophageal lesions during EGD, uncertainties in the proper diagnosis of GERD, or persisting symptoms on PPI therapy despite endoscopic diagnosis of ERD, esophageal physiological tests are recommended [12, 13]. Diagnostic criteria and cutoff values for esophageal reflux monitoring have been published previously [11, 14, 15].

In daily practice, there are still some uncertainties when to send patients for reflux monitoring or upper endoscopy, i.e. on PPI treatment or after having stopped a previously started antisecretory medication. Therefore, an international consensus group of experts

Fig. 1. Clinical spectrum of GERD phenotypes defined by endoscopy and esophageal reflux monitoring (modified from [21]).

in the field updated the recommendations regarding indications, interpretation, diagnosis, and classification of GERD subtypes [16, 17]. One of the most important advances in clinical decision making and management is the differentiation of patients with unproven GERD and proven GERD in patients with endoscopic or physiological evidence of GERD, which directs esophageal reflux monitoring on or off PPI therapy.

Within this article, we discuss the major issues and aims as well as recommendations for daily clinical practice that are delineated in this updated consensus of dedicated experts.

GERD Phenotypes

Traditionally, GERD phenotypes are endoscopically defined as ERD in the presence of esophageal lesions and NERD in case of endoscopically normal appearing mucosa of the distal esophagus. The presence of normal appearing esophageal mucosa in up to 70% of the patients with GERD symptoms (included under the umbrella term of ‘NERD’) documents the high specificity but low sensitivity of endoscopy for GERD diagnosis [18, 19]. In case of a normal appearing gastroesophageal junction, ambulatory reflux monitoring is mandatory to detect pathological esophageal exposure to gastric contents and association of symptoms with reflux episodes (symptom association probability (SAP) > 95% and symptom index (SI) > 50%) [19, 20]. According to the Rome IV criteria, GERD phenotypes are characterized in patients with:

- (1) ERD when having erosive esophagitis,
- (2) ‘true’ NERD documented by means of pathological acid exposure time in ambulatory pH monitoring,
- (3) patients with esophageal hypersensitivity (normal acid exposure but positive symptom association), and
- (4) patients with functional heartburn other differential diagnosis (normal acid exposure and no symptom association) (fig. 1) [21, 22].

Definition of Distinct Clinical Settings of Unproven and Proven GERD

Due to the high prevalence of typical GERD symptoms in Western world communities [1, 2], patients suffering from typical symptoms are initially managed empirically with PPI. Responsiveness to empiric PPI therapy in this clinical situation of unproven GERD predicts a high likelihood that these patients suffer from symptomatic GERD. Though a sensitivity of around 80% can be stated, the specificity of the so-called ‘PPI test’ to predict mucosal lesions of erosive esophagitis or an abnormal acid exposure in physiological reflux testing is low (50–60%) [23, 24].

Atypical symptoms, persisting symptoms despite adequate PPI therapy, or the presence of alarm symptoms demand further diagnostic steps starting with EGD, with biopsies to rule out other diseases, such as eosinophilic or infectious esophagitis or other mucosal processes. Persisting symptoms as well as atypical symptoms also necessitate ambulatory reflux monitoring to confirm or exclude the proper diagnosis of GERD.

Summarizing most clinical scenarios, ambulatory reflux monitoring has finally to rule out or confirm abnormal reflux burden to the distal esophagus [25]. The question to be answered by the clinician is when and how to perform reflux monitoring (*on* or *off* PPI; pH-metry or pH-impedance), and finally led to the concept of unproven and proven GERD in the consensus statement [16].

Unproven GERD is thereby defined as the absence of prior evidence of GERD, i.e. no prior endoscopic evidence (erosive esophagitis > Los Angeles classification grade B; stricture; Barrett’s esophagus) and no prior abnormal ambulatory reflux monitoring. The question to be answered is if the patient is properly diagnosed as suffering from GERD. Esophageal reflux testing in these patients should be performed *off* PPI therapy. Similarly, evidence of GERD needs to be proven before antireflux surgery. Surgical guidelines recommend to stop a current PPI therapy at least 7–10 days prior to testing [26].

Fig. 2. Clinical scenarios and diagnostic algorithm in case of GERD symptoms according to the updated Porto consensus statement (modified from [17]).

Repeated or prolonged wireless pH-metry can be considered in case of a strong clinical suspicion and a previous negative reflux testing because of a day-to-day variability of reflux testing, and prolonged analysis can further increase the diagnostic yield [15, 27].

In contrast, proven GERD is defined by prior endoscopic evidence of GERD or a prior abnormal reflux testing. The objective answered by ambulatory reflux monitoring in these patients is to determine if persisting symptoms can be linked to ongoing reflux episodes under PPI therapy; mainly weekly acidic reflux episodes are supposed to induce symptoms [28, 29]. In this clinical scenario, classic pH-metry is not sufficient to answer this question, and pH-impedance *on* PPI therapy should be performed.

Figure 2 summarizes the clinical scenarios and diagnostic algorithm in case of GERD symptoms with regard to proven GERD and unproven GERD and monitoring *on* or *off* PPI therapy.

Mucosal Changes and Additional Impedance Metrics in the Differential Diagnosis of GERD

Esophageal mucosal changes such as dilated intercellular spaces, basal cell hyperplasia, and papillary elongation have been described in patients with GERD and have been linked to a reduced transepithelial resistance and higher epithelial permeability [30, 31]. Esophageal biopsies evaluating these changes in patients with suspected GERD have demonstrated moderate to good sensitivity and specificity [32]. By calculating a global score of these distinct changes, the definition of ‘microscopic esophagitis’ has been used to distinguish patients with NERD from patients with functional heartburn as well as healthy controls with good accuracy [6, 7]. Conversely, there are some restrictions, mainly because of low

specificity of these morphological changes and variations of intra- and interobserver agreement between pathologists, which limit the use of histopathological assessment of GERD in clinical practice [33, 34]. Mean baseline mucosal impedance signals, especially when measured during nighttime without swallow-associated artefacts, are inversely correlated with esophageal acid exposure and morphological changes, such as dilated intercellular spaces. Low baseline impedance values are supposed to correlate with impaired mucosal integrity and transepithelial permeability [35, 36]. Lower baseline impedance values (<2,000 Ω) have been found in patients with proven GERD (ERD and NERD) and have been demonstrated to distinguish from patients with functional heartburn [37–39]. Therefore, analysis of mean baseline impedance values is discussed as a complementary tool during pH-impedance monitoring.

Conclusion

Evidence from clinical studies and modern tools in the diagnostic workup of GERD have specified the clinical spectrum and phenotypes of GERD. Diagnostic algorithms have been proposed in a consensus statement of leading experts in the field. Different clinical scenarios have been defined for the use of various reflux monitoring modalities (pH-metry, pH-impedance), distinct cutoffs of the metrics have been stated, and a clear statement has been made when to perform reflux monitoring *on* or *off* PPI therapy.

Disclosure Statement

None of the authors has financial or other relations to declare.

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