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Testing for refractory gastroesophageal reflux disease



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Abstract

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. Although proton pump inhibitors (PPIs) are proven to be effective in the treatment of GERD, inadequate symptom response to once daily, and according to some, twice-daily dosage is accepted as refractory GERD. Non-erosive reflux disease (NERD) patients are less likely to respond to treatment with acid suppressive therapy. The increasing number of patients with persistent symptoms on acid suppressive therapy presents a challenge to gastroenterologists. Ambulatory esophageal pH and/or impedance monitoring is a commonly used test in refractory GERD, which can help in determining esophageal acid exposure and number of reflux events and the relationship between symptoms and reflux events. In this review, we will discuss the role of diagnostic testing and answer questions such as whether to test this group of difficult to treat patients on or off PPI therapy.

Introduction

GERD is generally a chronic condition that occurs when gastric contents, including gastric acid, pepsin and pancreatobiliary secretions, regurgitate into the esophagus causing symptoms and/or injury in the esophagus or the upper aerodigestive tract[1]. It is a common disease, affecting 30% to 40% of the U.S. population in their lifetime, while 5% to 25% of the worldwide population has some symptoms of GERD in a 3-month period[2]. In addition to its negative impact on health related quality of life[3-5], GERD may lead to serious sequelae, including esophagitis, strictures, ulcers or Barrett's esophagus[6].

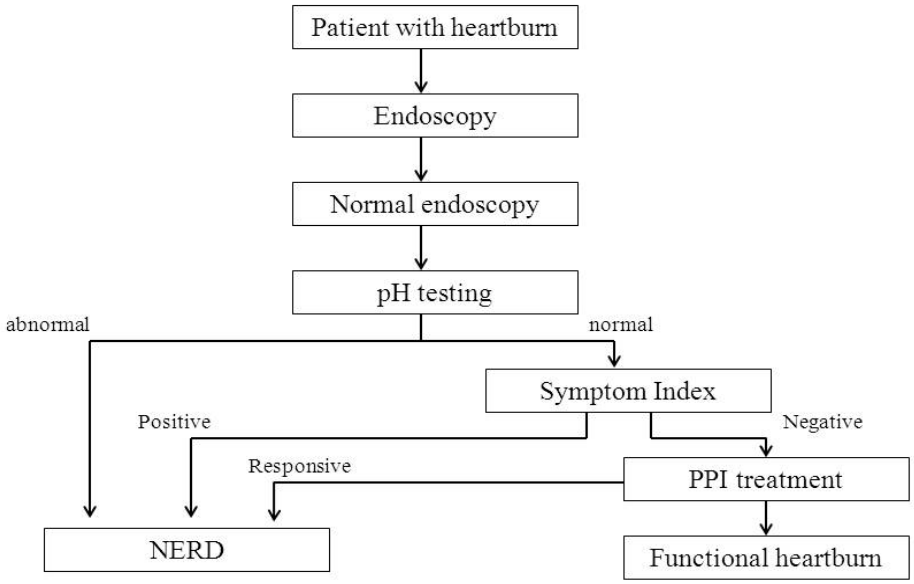
Since their introduction into the market almost two decades ago, PPIs have revolutionized the treatment of GERD[7]. Despite their high degree of efficacy, it is reported that approximately 30% (range: 10-40%) of patients with GERD fail to respond symptomatically to a standard-dose PPI, either partially or completely. Of these, most patients will continue to have GERD symptoms even on higher doses of PPI. The most common presentation of GERD in gastrointestinal practice has now become the failure of PPI treatment in resolving GERD associated symptoms[7,8].

In patients with refractory GERD, pH and/or impedance monitoring is recommended to assess the degree of acid suppression, to confirm the diagnosis, to evaluate any correlation of symptoms and reflux, and to decide whether further treatment is indicated. This paper will focus on refractory GERD and the role of pH/impedance monitoring testing in these patients.

Definition of refractory GERD

Regurgitation and heartburn, described as a burning sensation radiating up from the sternum, are the typical symptoms of GERD, but GERD can also be associated with quite heterogeneous symptom complex and atypical manifestations, such as pulmonary disease (asthma), cough, noncardiac chest pain, reflux laryngitis and dental erosions[9-11]. GERD may produce esophageal erosions, but a significant proportion (50-70%) of patients with GERD do not have evidence of erosive changes on endoscopy. These "endoscopy-negative" patients with typical GERD symptoms are classified as non-erosive reflux disease (NERD) group [12,13]. Based on the Rome III criteria for functional esophageal disorders, patients with NERD are distinct from those with functional heartburn (Figure 1). Patients with a high esophageal acid exposure time (AET) are classified as having true NERD. Patients with a normal AET but a positive symptom correlation profile using the symptom index (SI) and/or symptom association probability (SAP) scores are referred to as having an acid-sensitive esophagus within the NERD spectrum. Conversely, patients with a normal AET and negative symptom correlation are classified as having functional heartburn[14]. Epidemiologic studies investigating patients with GERD-related symptoms have suggested that the prevalence of NERD in the general population is between 50% and 70%[15,16].

Figure 1. A diagnostic algorithm of NERD and functional heartburn based on ROME III criteria.



PPIs are currently considered as the most effective and safe therapeutic modalities for GERD, however up to 15% of patients with erosive esophagitis (EE) continue to report GERD symptoms despite complete mucosal healing. It is known that esophageal acid exposure is a dose-dependent phenomenon, and increasing a PPI dose to b.i.d. will normalize the pH parameters in the majority of patients with either typical or extraesophageal symptoms[17]. It is, therefore, reasonable to ask whether a standard dose PPI is sufficient to be considered as a PPI failure. Some authors propose a full course of standard dose PPI (once a day)[7, 18, 19] while other authors believe that GERD patients who exhibit partial or lack of response to PPI twice daily should be considered as PPI failures [17, 20-22]. Furthermore, it is unclear what symptom burden during PPI consumption fulfills the definition of refractory GERD[20]. Because refractory GERD is a patient-driven event, PPI failure patients who search for medical care will present different frequency and/or severity of GERD-associated symptoms[8]. The American Gastroenterological Association recommended twice-daily PPI therapy for reflux patients with an inadequate symptom response to once-daily PPI therapy and to accept the situation as treatment failure after heartburn has not adequately responded to twice-daily PPI therapy[23].

Table 1: Reasons for proton pump inhibitor-refractory reflux symptoms

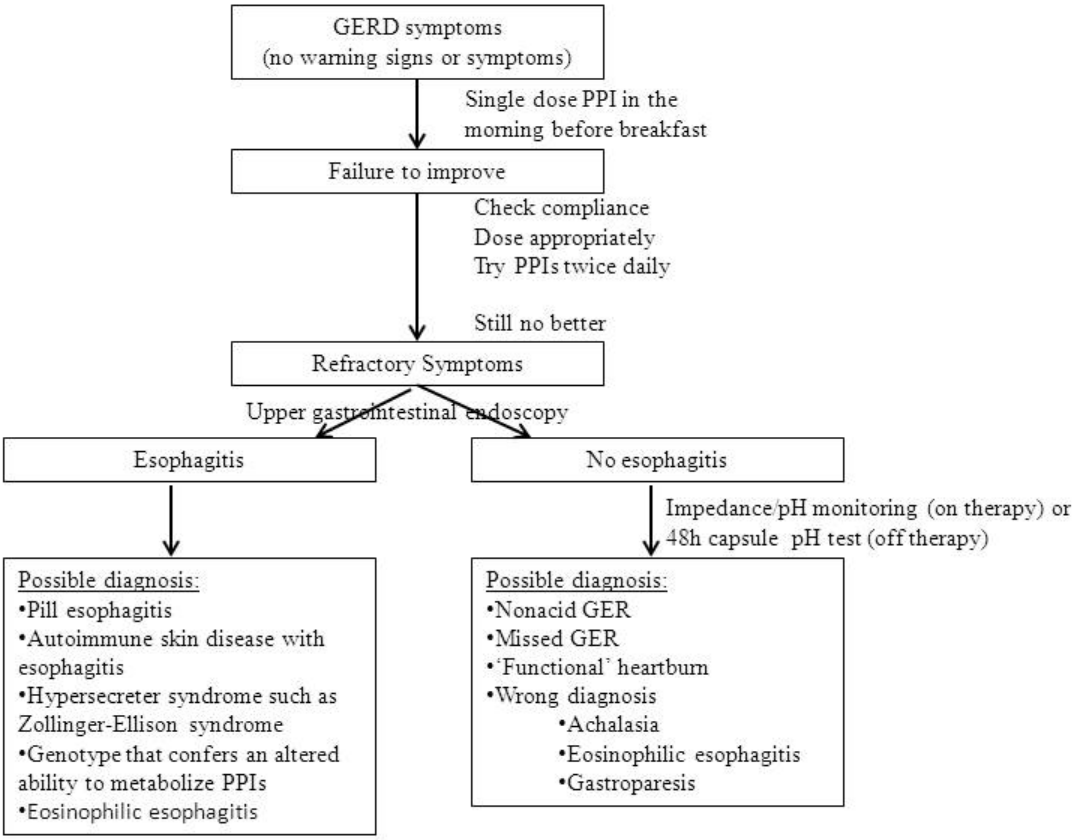
No gastroesophageal reflux disease (GERD)
Functional dyspepsia
Rumination syndrome
Aerophagia
Achalasia
Eosinophilic esophagitis
Insufficient acid suppression
Lack of compliance
Genetic variation (±) (Helicobacter pylori)
Zollinger-Ellison syndrome
Insufficient duration of treatment (nocturnal acid breakthrough)
Nonacid reflux
Esophageal hypersensitivity

The emphasis on acid suppression has resulted in the misconception that GERD is associated with increased esophageal exposure to only gastric acid, whereas other components of refluxed gastric juice have been ignored[24]. NERD that is resistant to high dosages of PPI may be attributed to the gastro-esophageal reflux of noxious substances other than hydrochloric acid such as bile acids[25], with one study showing that 76% of patients with symptomatic reflux had abnormal esophageal exposure to both acid and bile reflux, which occurred simultaneously in 70%–91% of reflux episodes and more severe forms of GERD had increasingly higher (89%–100%) exposure to the simultaneous damaging effect of acid and bile than those with less severe forms of GERD[26]. In addition, visceral hypersensitivity, bile reflux, delayed gastric emptying, eosinophilic esophagitis, psychological co-morbidity and potentially other mechanisms have been suggested as an explanation for PPI failure (Table 1)[27-30].

Testing in refractory GERD

Upper endoscopy is indicated to rule out complications such as Barrett's esophagus in patients with persistent symptoms, despite therapy and those with alarm symptoms, such as dysphagia, weight loss, bleeding or a long history of GERD[11]. In patients with refractory GERD symptoms despite PPI use but without alarm symptoms, the first consideration should be given to patient compliance and the correct timing of the PPI dose (Figure 2). For example, it is essential that patients take their PPI's 30-60 minutes prior to meals if delayed release formulation is prescribed. If patients are on once daily PPI therapy, most clinicians would increase this medication to twice daily dosing, since physiologic studies show that up to 40% of patients may still have abnormal esophageal acid exposure on once daily therapy[17]. If patients remain symptomatic despite higher PPI dosing, diagnostic testing is indicated. An upper endoscopy is performed to assess the presence or absence of esophagitis and to exclude other possible diseases such as refractory peptic ulcer and eosinophilic esophagitis (Figure 2)[22]. Esophagitis on endoscopy is a highly specific sign for GERD. Patients who have a normal endoscopy account for approximately 90% of all patients with refractory GERD[22], which makes testing for GERD a challenge. In general, the value of endoscopy in discovering GERD-related findings in patients with refractory patients is very low[20]. NERD patients refractory to PPI should undergo further tests, including prolonged pH monitoring, impedance testing for nonacid gastroesophageal reflux, esophageal manometry and gastric function testing and should be searched for nonacid GER or missed acid gastroesophageal reflux, functional heartburn, or diseases such as achalasia or gastroparesis (Figure 2).

Figure 2. A potential treatment and test approach for patients with suspected refractory GERD



The role of esophageal biopsies during endoscopy in refractory GERD is somewhat controversial. If patients complain of dysphagia and there is evidence of esophageal narrowing, it is reasonable to perform esophageal biopsies to evaluate for eosinophilic esophagitis, which commonly presents with rings and furrows at endoscopy (Figure 3). Recent studies have focused on the role of histology for evidence of inflammation and/or dilated intercellular space in diagnosing continued reflux in those with suspected refractory GERD[24, 31-33]. Oh et al. showed that esophageal mucosal integrity might have been damaged even when the esophageal mucosa seems normal on endoscopy. When biopsied, over one third will have evidence of inflammation on histology, and of these, 80% will have a defective LES. The presence of dilated intercellular spaces in the esophageal mucosal biopsy is also suggested as a sensitive marker of GERD. Until further evidence, esophageal biopsies should be reserved to those in whom eosinophilic esophagitis is suspected.

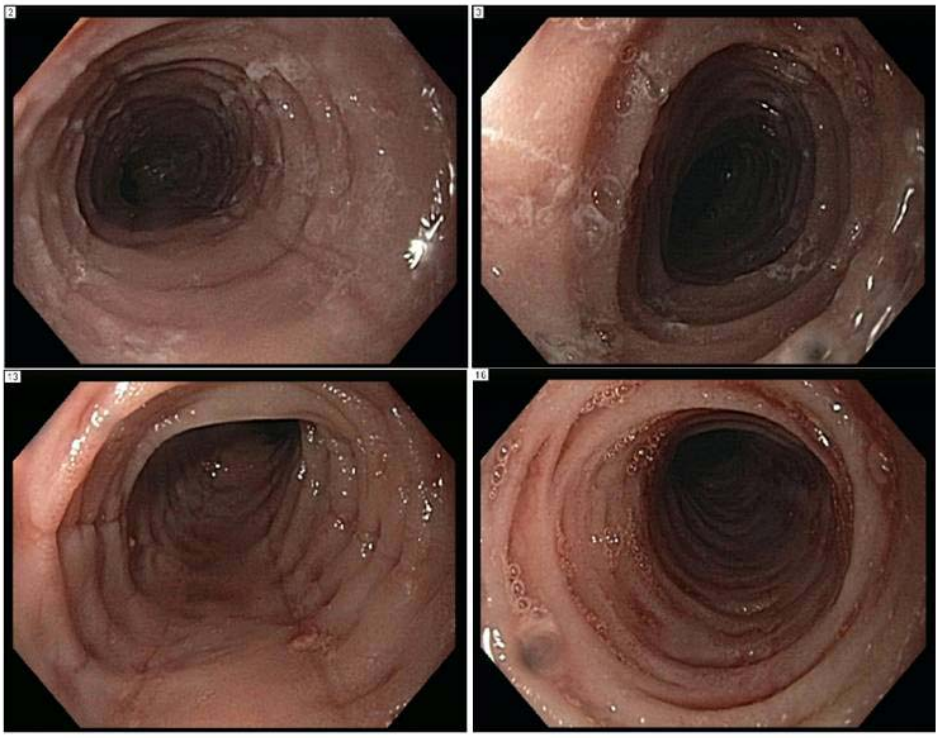


Figure 3. Endoscopic view of the mid esophagus showing ringed appearance to the esophageal lumen with furrows diagnostic of eosinophilic esophagitis.

The indications for esophageal pH testing are listed in Table 2. Lack of response to an empiric trial of PPI therapy (refractory symptoms) in patients with typical or atypical (extraesophageal) symptoms is the most common indication in performing ambulatory pH testing[34]. Esophageal pH monitoring was the first method quantifying gastro-esophageal refluxate, independent of mucosal lesions and evaluating the relationship between symptoms and reflux episodes[35-40]. More recent advances in ambulatory esophageal monitoring include: wireless esophageal[41] and oropharyngeal[42,32] pH monitoring devices, esophageal bilirubin monitoring[26] and combined multichannel intraluminal impedance–pH monitoring[44,45]. Besides their strengths, each technique has its limitations that clinicians and investigators should be aware of when choosing a test in a particular patient[35] (Table 3).

Table 2. Indications for esophageal pH monitoring.

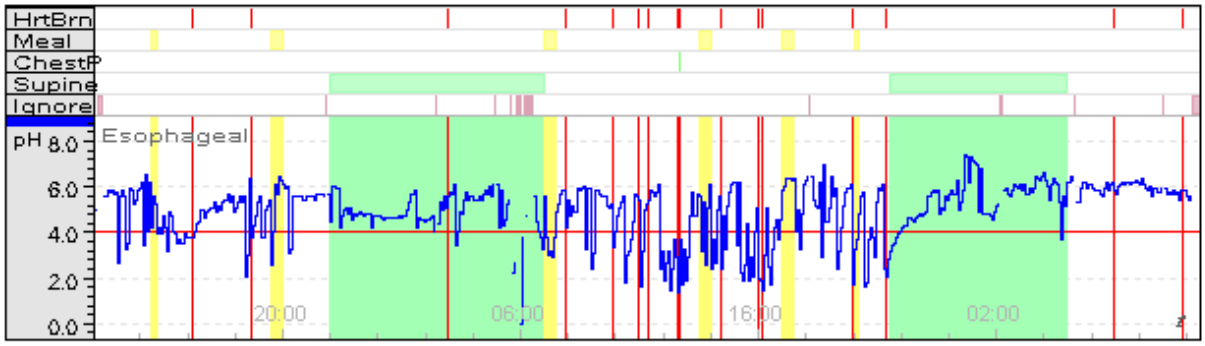
1. Patients with typical GERD symptoms who fail 4 weeks of PPI therapy
2. Patients with atypical symptoms who fail 6 to 8 weeks of PPI therapy
3. Patients being considered for endoscopic or surgical reflux therapy
4. Patients who have undergone endoscopic or surgical reflux therapy and who continue to have GERD symptoms

Table 3. Advantages and disadvantages of commonly employed methods employed in refractory GERD.

Method	Advantages	Disadvantages
Endoscopy	Easy visualization of mucosal damage/erosions	Poor sensitivity/specificity/PPV Requires sedation High cost
pH Monitoring	Easy to perform Relatively noninvasive Prolonged monitoring (24-96 hours) Ambulatory	May be catheter- or wireless-based May have up to 30% false negative rate (less in the wireless based system)
Impedance Monitoring	Easy to perform Relatively noninvasive Prolonged monitoring Ambulatory Measures acidic and non-acidic gas and liquid reflux (combined with pH)	Catheter based False negative rate unknown but most likely similar to catheter based pH monitoring Unknown clinical relevance when abnormal on PPI therapy Unknown importance in refractory GERD
Bilirubin monitoring	Fast and easy detection of bilirubin as a surrogate marker for bile reflux Acceptable sensitivity and specificity	Catheter based Not widely available Underestimates bile reflux in acidic environment
ResTech Dx-pH (oropharyngeal pH)	Faster detection rate and faster time to equilibrium pH than traditional pH catheters Increasingly employed in patients with extraesophageal reflux	Catheter based Unknown if clinically useful in patients with patients with extraesophageal reflux

Esophageal pH monitoring *off therapy* is commonly used to determine if the patients' suspected initial diagnosis of reflux disease is accurate. It may also be used to assess if persistent symptoms on therapy are due to continued esophageal acid exposure, in which case the test is performed *on therapy*. There are six parameters that are often analyzed during esophageal pH monitoring to determine if a patient has abnormal esophageal reflux (Figure 4) (Table 4). The most commonly used parameters are either the percent total time pH < 4[39] or the DeMeester Score (a composite score using the mean values for the above parameters with abnormal being > 22)[36]. In addition to the actual pH parameters measured during the monitoring period, other indices can correlate patient symptoms to actual reflux observed during pH monitoring. These symptom indices are important components of assessing the relationship between reflux and patients typical (heartburn, regurgitation) or atypical (chest pain, cough, wheezing) symptoms. The two most commonly employed symptom indices include: *symptom index (SI)*, and *symptom association probability (SAP)*. They are calculated using the data obtained from 24- or 48-hour pH monitoring and using the patient's diary of symptoms (Figure 4). These indices emphasize the importance of an accurate patient diary that records symptom timing and marks these symptoms by pushing the recorder button. However, the reproducibility and accuracy of both SI and SAP have recently been questioned in those with refractory symptoms[46].

Figure 4. Wireless pH tracing of abnormal esophageal acid exposure. This patient has abnormal upright and supine reflux as the percentage of time pH <4 is abnormal. There is a positive symptom index for chest pain and heartburn and positive symptom association probability for heartburn.



Reflux Table - Acid Reflux Analysis- Day 1

	Total	(Normal)	Upright	(Normal)	Supine	(Normal)
Fraction Time pH <4 ((%))	7.2	5.5	8.9	8.2	4.6	3.0
Number of Refluxes	65		47		18	
Number of Long Refluxes(>5 (min))	5		3		2	
Duration of longest reflux (min)	9		9		9	
Time pH <4 ((min))	95		72		23	

SI Table - Acid Reflux Analysis

	Total
HrtBrn	50.0
Regurg	n/a
ChestP	100.0

Reflux Table - Acid Reflux Analysis - Day 2

	Total	(Normal)	Upright	(Normal)	Supine	(Normal)
Fraction Time pH <4 ((%))	10.9	5.5	14.4	8.2	4.6	3.0
Number of Refluxes	42		37		6	
Number of Long Refluxes(>5 (min))	8		8		1	
Duration of longest reflux (min)	30		20		19	
Time pH <4 ((min))	136		115		20	

SAP Table - Acid Reflux Analysis

	Total
HrtBrn	100.0
Regurg	0.0
ChestP	76.9

Table 4. Normal values for 24H esophageal pH monitoring

	1974	1992
	(Johnson/DeMeester)	***(Richter et al.)***
1. % of Total period pH<4:	< 4.2%	< 5.78%
2. % of Supine period pH<4:	< 1.2%	< 3.45%
3. % of Upright period pH<4:	< 6.3%	< 8.15%
4. Total number of reflux episodes:	< 50	< 46
5. Total number of reflux episodes >5 min:	< or = 3	< 4
6. Length of longest episode of reflux:	< 9.2min	< 18.45min

Although it was once considered as the gold standard for detecting esophageal acid exposure, studies have demonstrated that the sensitivity of 24-hour pH monitoring (70%-80%) is not as high as expected. The false-negative rate for this test may range from 20% to 50%. A negative test may not exclude the diagnosis of GERD, whereas a positive test does not confirm that GERD is the etiology for the symptoms, and atypical/ extraesophageal symptoms are even more of a problem because sensitivity of the proximal probes are even lower (50%)[11, 47, 48]. Additional limitations of conventional pH testing include the reduced patient physical and dietary activity during the recording period owing to nasal and pharyngeal irritation of the pH catheter and the day-to-day variability in acid exposure.

Given the above limitations with the catheter-based pH testing, wireless ambulatory pH capsule was developed, which is safe and effective in monitoring esophageal acid exposure for 48- or 96-hours[49]. Since no catheter is required, it has improved patient tolerance and may have less influence on daily-life parameters, such as mobilization and eating habits[50, 51]. An alternative to pH probe most recently introduced is the Restech pH, which is positioned in the oropharynx to measure pharyngeal acid exposure for patients with suspected extraesophageal reflux symptoms, such as asthma, cough or laryngitis. This probe is a new, potentially more sensitive and minimally invasive device, which is capable of detecting liquid or potentially aerosolized droplets. Initial studies with this device are encouraging [42,43], and future studies in patients with refractory symptoms are needed.

Employing catheter based pH monitoring, Charbel et al. found that 31% of the patients with typical symptoms and 30% of those with extraesophageal symptoms had abnormal pH monitoring when treated with once daily PPI, while only 7% and 1% of patients; respectively had abnormal pH on b.i.d. PPI[17]. This study underscores two important facts about patients with persistent symptoms despite PPI therapy: 1) once daily therapy is not adequate in controlling esophageal acid exposure in some patients, thus the need for increasing PPI frequency to twice daily and; 2) on twice daily PPI dosing, continued acid reflux does not appear to be the driver of continued symptoms in patients with refractory GERD.

PPIs only change the pH of the refluxate but do not reduce reflux itself; the total number of reflux events stays unchanged. PPI therapy does not prevent the reflux of weak acid and bile with the potential for ongoing tissue injury and nonacid reflux, which may still play an important role in persistent symptoms of reflux[24,52]. A bilirubin monitoring device, such as the Bilitec, was employed in

the mid 1990's as a surrogate marker for esophageal exposure to bile acids. Studies employing this device suggested that acid and bile commonly reflux together and may contribute to symptoms and esophageal mucosal injury[26], and PPI therapy not only reduces acid but also decreases esophageal bile exposure[53]. With the advent of impedance-pH monitoring, clinical utility of bilirubin monitoring has decreased; however, given the increasing prevalence of patients with refractory GERD, it may be making resurgence. A recent study using simultaneous 24-hour ambulatory pH and Bilitec monitor in patients with persistent heartburn or regurgitation despite standard PPI doses, found that only 11% had pathological acid exposure, 38% had pathological bile exposure, and 26% had pathological exposure to both acid and bile. Acid exposure was positive in 37%, but adding Bilitec increased the diagnoses of persistent reflux to 75%. In patients with poorly responsive reflux disease, a combined pH and Bilitec monitoring may be superior to pH monitoring alone[19].

Impedance–pH is the latest technique used for evaluation of GERD and esophageal function. It uses inherent conductive or resistive properties of the intraluminal bolus (liquid, gas, or mixed) to examine the presence and transit of the bolus in the esophageal lumen. It is useful in evaluating patients with persistent symptoms on acid-suppressive therapy, clarifying the effectiveness of acid suppression by assessing distal esophageal acid exposure, while also providing information on any relationship between gastro-esophageal reflux of any type (acid, non-acid, liquid, mixed, gaseous) and associated symptoms[35,44]. It is also helpful in demonstrating the proximal extent of reflux into the esophagus and the presence of gas reflux episodes with weak acidity that may underlie persistent reflux symptoms[44,54]. While up to 90% of patient with erosive esophagitis will achieve endoscopic healing, 35% will have persistent symptoms despite PPI therapy[55], which may be due to non-acid reflux[56].

In a systematic review of 21 studies, the majority of reflux episodes in patients with GERD taking a PPI were of pH >4, that is, weakly acidic or weakly alkaline and only a small proportion of reflux episodes were acidic. In a different study[21], 31% of patients with refractory symptoms on PPI therapy had non-acid reflux associated with continued symptoms. Based on multivariable analysis in a group of patients with persistent symptoms, two studies[57,58] suggested that reflux episodes extending proximally and having a mixed (liquid-gas) composition may be significantly associated with symptoms irrespective of whether the pH is acid or non-acid. Studies have shown that in patients with NERD, the presence of gas in the refluxate significantly increased the probability of reflux perception. These patients were also more sensitive to less acidic reflux than esophagitis patients. The role of non- or weakly acid reflux as the etiology for refractory symptoms continues to be debated. Some have suggested a role of referring patients to undergo surgical fundoplication based on impedance-pH findings[59], while we suggest caution in recommending surgical intervention in this group of patients[60].

pH testing: *on versus off* PPI therapy

In patients refractory to PPIs, controversy exists whether pH testing is more useful while *on* or *off* therapy [61,62]. In patients with refractory symptoms despite twice daily PPI therapy, testing on therapy provides information whether acid or non-acid reflux continues to be present. Studies in this regard suggest that up to 37% of patients on twice-daily therapy will have abnormal non-acid reflux[21] but greater than 90% will have normalized esophageal acid exposure[17]. Thus, on-therapy testing will be normal in the majority of patients (63% to 90%) refractory to PPI therapy, and a search for non-GERD causes should be initiated. The criticism of this approach is that we will not know if the patient has reflux at baseline. The counter argument to this criticism would be that knowledge of baseline reflux status in this group of patients does not help answer why they continue to have symptoms while on twice-daily PPI therapy. Off-therapy testing advocates argue that normal esophageal reflux parameters at baseline would exclude the likelihood that the patients' symptoms are reflux related.

However, a recent study suggests that the majority (72%) of patients' refractory to twice-daily PPI therapy would actually have abnormal esophageal acid exposure if tested off PPI therapy[63]. In this case, off-therapy testing only confirms GERD but does not explain the persistence of symptoms while on therapy.

Until we have better outcome data and given effectiveness of empiric therapy, I recommend using patients' response to aggressive acid suppressive therapy as the guide to whether or not GERD might be playing a role in their symptom complex. Complete lack of response to twice-daily PPI therapy should sounds clinical alarms about the causal association between reflux and patients' complaints. The value of testing with esophageal pH or impedance monitoring in patients refractory to twice-daily PPI therapy is often not in identifying reflux as the cause for patients' persistent symptoms; rather, it is to document that GERD is not the cause, and a search for non-GERD causes should be pursued.

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