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Ambulatory reflux monitoring in GERD – Which test should be performed and should therapy be stopped?

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Abstract

Diagnosing gastroesophageal reflux disease (GERD) often entails using a combination of patient symptoms, response to proton pump inhibitors (PPI), upper endoscopy, and ambulatory reflux testing. Each of these has limitations which the clinician must be aware of when managing patients with reflux symptoms. Ambulatory reflux monitoring, in particular, can potentially document the true presence of pathologic GERD. Consequently, reflux testing is often necessary in our evaluation of patients with reflux symptoms and can be useful in distinguishing etiologies driving a lack of response to PPI therapy. Reflux testing results can be also used to guide appropriate PPI prescribing and clinical decision making for appropriate or unnecessary therapy. This review focuses on the limitations of our current diagnostic paradigm and highlights how reflux testing can be helpful in the diagnosis and management of patients with poor response to PPI therapy.

Keywords

gastroesophageal reflux disease; reflux monitoring; proton pump inhibitor; heartburn; pH testing; impedance; endoscopy

I. INTRODUCTION

The requirement of reflux testing in gastroesophageal reflux disease (GERD) can be determined by analyzing the Montreal consensus definition which describes a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.[1] In order to diagnose and distinguish GERD one must be able to confidently identify pathologic gastroesophageal reflux using a gold standard to either “rule in” or “rule out” GERD as the cause of the current symptoms. Unfortunately, there is no gold standard in GERD diagnosis and what we are left with is our best guess based on a combination of factors: patient symptoms, response to PPI, endoscopy and reflux testing. Each of these factors is helpful in specific scenarios and they may be useful by themselves in instances where patients present with endoscopic findings that are synonymous with GERD, including severe erosive esophagitis and/or long segment Barrett’s esophagus. However, abnormal endoscopic findings are less common these days due to widespread PPI use and we are more commonly faced with the dilemma of patients who are not responding to PPI therapy in the context of a normal endoscopy. The current paradigm for evaluating these patients revolves around reflux testing as this tool can potentially document the presence of pathologic gastroesophageal reflux and distinguish functional heartburn from GERD. Consequently,

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reflux testing is necessary in our evaluation of patients with GERD symptoms, but it is not a gold standard and should never be considered as a substitute for good clinical judgment. This review will focus on the limitations of our current diagnostic paradigm and highlight how reflux testing can be helpful in the diagnosis and management of patients with poor response to PPI therapy (PPI non-responders).

II. CURRENT DIAGNOSTIC PARADIGM FOR REFLUX SYMPTOMS

The algorithm for managing patients with retrosternal discomfort/chest pain and/or regurgitation is presented in Figure 1a and represents a modification of the diagnostic paradigm presented by Kahrilas and Smout in 2010.[2] The diagnoses are determined by a combination of the presenting symptoms and various diagnostic tests ranging from a simple empiric PPI trial to invasive tests. Components of this paradigm focused on reflux testing will be evaluated separately regarding the strengths and limitations of the approach and how the methodology can be leveraged to help improve diagnosis and management.

IIa. Symptom Presentation

Symptoms of heartburn and regurgitation have a much lower specificity than previously believed. Dent et al. evaluated the accuracy of a validated questionnaire (Reflux Disease Questionnaire - RDQ), family practitioners, gastroenterologists, and a trial of PPI therapy in diagnosing GERD.[3] Patients received endoscopy and 48hr pH monitoring to determine the presence or absence of GERD. Patients were given a diagnosis of GERD if they had at least one of the following: 1) Any grade of reflux esophagitis 2) esophageal pH <4 for >5.5% time 3) positive symptom association probability (SAP >95%) with reflux and 4) borderline acid (pH<4 3.5–5.5% time) AND positive response to esomeprazole treatment.[3] Overall, the RDQ, family physicians, and gastroenterologists had similar sensitivity (62%, 63%, 67% respectively) and specificity (67%, 63%, 70% respectively) in diagnosing GERD. Notably, symptom response to PPI therapy did not improve diagnostic accuracy, indicating that a symptom based assessment in patients with reflux symptoms is important in making the diagnosis.

Another recent study has evaluated the association between a widely used symptom based diagnostic questionnaire (the GerdQ) and 48-hr wireless pH monitoring in patients both off and on PPI therapy.[4] Strengths of this study include a prospective design and large number of enrolled patients (175 patients on PPI and 178 off PPI therapy). Higher GerdQ scores were predictive of an abnormal pH study in patients off PPI therapy, but overall, the symptom based questionnaire had only modest accuracy in diagnosing GERD. Of note, the questionnaire was not associated with an abnormal pH study or high symptom association probability (SAP 95%) in any patients on PPI therapy.[4] The authors concluded that the GerdQ is not an accurate tool for diagnosing GERD and recommended that pH testing should be performed only off PPI therapy in patients with a low pre-test probability of GERD.

Other investigators have evaluated the additional use of low distal baseline impedance measurements in evaluating the specificity and sensitivity of symptoms in diagnosing GERD. A small study of 70 consecutive NERD (44 PPI responders, 26 PPI non-responders, 10 healthy volunteers) patients with MII-pH testing evaluated the correlation of symptoms with low baseline esophageal impedance measurements.[5] They found that these baseline measurements did not predict PPI response or symptom perception. Of note, Heard et al. found in a retrospective review of 2809 patients that only 38 patients (1.4%) had low distal baseline impedance measurements raising concerns about the clinical utility of this measurement for diagnostic purposes.[6]

A robust clinical history is important when evaluating patients for a possible GERD diagnosis. Despite the limitations described above, the use of validated questionnaires and focused questions provides structured assessment of symptoms with little harm to the patient, minimal cost, and with performance characteristics on par with medical specialty care. However, clinicians should be mindful that symptoms alone are not good enough to predict a definitive GERD diagnosis or response to therapy.

IIb. Response to empiric PPI therapy

A very recent study reevaluated data from the well-known DIAMOND study[3] to assess the ability of the PPI "test" to identify patients with GERD. The authors included patients diagnosed with GERD according to study protocol (criterion included pH testing and positive response to esomeprazole treatment).[7] Of the 203 patients diagnosed with GERD, only 9 patients had a diagnosis based exclusively on response to PPI therapy. Also, a substantial number of patients (up to 62%) without GERD had symptom response with PPI therapy and physicians were not able to predict which patients would respond to a PPI. The authors conclude that the PPI test adds very little information in distinguishing patients with and without GERD.[7] Interestingly, in those patients with symptomatic relief from a PPI the time to response was seen predominantly in 5–7 days. The AGA position statement on GERD treatment does not actually specify an exact time duration for empiric therapy but common practice is 4–8 weeks.[8,9] We have found that many patients continue empiric PPI therapy even after negative results from reflux testing.[10] As the most recent data suggests that a PPI test is equivocal in the majority of patients, shorter durations of empiric therapy are not unreasonable. As shown in Figure 1b, a reasonable daily PPI trial would be 2–4 weeks. If symptoms are still present, physicians should assess patient compliance and increase the PPI dose for a short period of time (2 weeks) prior to further evaluation and diagnostic testing. A primary issue of this algorithm is that the burden falls on the physician to assess response in a timely fashion so patients do not continue medications indiscriminately without appropriate follow up.

Even before one assesses the level of response, one would also have to document compliance to medical therapy at an appropriate dose sufficient to treat most grades of reflux severity. In evaluating the dose of proton pump inhibitor therapy that would reasonably be seen as a failure, one would likely utilize a dose that is higher than the current FDA-approved doses for the various available PPIs. Based on current treatment guidelines[8] and physiologic testing data available on patients on single dose therapy and on double dose therapy, a reasonable approach would be to consider patients who fail twice the FDA-approved dose in either a single dose or split (bid.) dose regimen as a failure. Most guidelines advocate for physiologic reflux testing after patients have attempted an escalation of PPI therapy to double dose.[8] In addition, studies assessing abnormal acid exposure on PPI therapy in patients with continued symptoms suggest that up to 30% of symptomatic patients on single-dose PPI therapy will have abnormal acid exposure. In contrast, less than 10% of symptomatic patients on double-dose PPI therapy will have abnormal acid exposure. Given that the primary mechanism of PPI therapy is to reduce overall acid reflux and reflux burden, it would appear that the yield of reducing acid burden by increasing the PPI dose to double the FDA-approved dose is significant and would warrant this degree of escalation as the threshold for someone to be considered a PPI failure. Thus, we would not recommend endoscopy or reflux testing in most patients with symptoms on standard daily doses as a proportion of patients will receive benefit from increased dosing.

IIc. Upper Gastrointestinal Endoscopy

GERD symptoms are the most common indication for upper endoscopy[11] and there has a been up to a 40% increase in the use of endoscopy among Medicare beneficiaries.[12] Upper

endoscopy can be revealing and guide management in patients with GERD and alarm symptoms (bleeding, dysphagia, anemia, weight loss, vomiting). Barrett's esophagus (BE) and esophageal adenocarcinoma are also concerns in certain patients (older age, male, white race) with chronic reflux symptoms.[12] However, symptoms alone do not predict BE, as men without symptoms have a much higher risk of BE than women with chronic reflux symptoms.[13] Also, follow up or repeat endoscopy is only recommended in patients with severe erosive esophagitis to document healing.[12] Prior work has shown that upper endoscopy is completely normal in 39% of patients with reflux symptoms and reveals erosive esophagitis in only ~28% of patients.[14] In addition, over 50% of patients who continue to have heartburn symptoms on once daily PPI therapy have been shown to have a normal endoscopy.[15] Upper endoscopy solely performed for reflux symptoms (with or without PPI therapy) is often negative and rarely changes the clinical management of these patients. Along with clinical predictors (symptoms) and empiric therapy, upper endoscopy falls well short of providing adequate sensitivity or specificity for diagnosing GERD.

One caveat to the use of upper endoscopy is our evolving understanding of the relationship between GERD, eosinophilic esophagitis (EoE), and PPI-responsive eosinophilia as recently reviewed.[16] The consensus recommendations for the diagnosis and management of EoE were recently updated to reflect the recognition of the overlap and potential co-existence of EoE and GERD.[17] Patients with a clinical history and symptoms suspicious for EoE, regardless of GERD symptoms, should undergo upper endoscopy with proximal and distal biopsies.[17] Patients with only refractory reflux symptoms may undergo endoscopy and it is certainly reasonable to rule out EoE, especially if endoscopic features are suggestive of the diagnosis. However, practitioners should be aware solid evidence is lacking to support endoscopic biopsies in every patient with refractory reflux symptoms to rule out EoE. Poh et al. retrospectively evaluated 105 Veterans who underwent endoscopy with biopsies for PPI "failure".[18] They found that EoE was found in in only 0.9% of patients. Other prevalence estimates of EoE in the US population range from 43–53/100,000 (~0.05%).[19] Miller et al. recently designed a Markov decision model and concluded that in patients with refractory reflux symptoms, upper endoscopy with biopsies to rule out EoE was cost effective when the prevalence of disease was ≥8%, which is significantly greater than current prevalence estimates.[20] In addition, the utility of ambulatory reflux monitoring (pH or pH-impedance) in EoE patients needs further study before this can be routinely recommended.

IId. Ambulatory Reflux Monitoring

As PPIs are extremely effective at healing virtually all esophagitis grades and virtually all patients referred for refractory GERD symptoms are taking or have taken PPI therapy, many patients will have a negative endoscopy as described above. Reflux monitoring can be performed to document pathologic acid gastroesophageal reflux in patients requiring evaluation for symptoms compatible with GERD (esophageal/extra-esophageal) in several circumstances as outlined previously[21] and described below.

Ambulatory reflux testing OFF medication

- Patients not fully responding to PPI therapy without a diagnosis of GERD based on endoscopy or a positive ambulatory test confirming pathologic acid gastroesophageal reflux.
- Pre-operative evaluation of patients prior to anti-reflux procedures (endoscopic/ surgical)
- Patients with persistent GERD symptoms after anti-reflux surgery.

Ambulatory reflux testing ON medication

- To assess adequacy of acid control in patients with complicated GERD, such as strictures and severe esophagitis.
- To assess a potential role of non-acid reflux in patients with a previously established diagnosis of GERD based on endoscopy or a positive ambulatory test confirming pathologic acid gastroesophageal reflux.

In particular, as shown in Figure 1c, when the pretest probability of GERD is low, wireless pH monitoring off medication is suitable and may aid in the diagnosis of functional heartburn. Patients that are able, should stop their PPIs 5–7 days prior to testing.[21] When probability of GERD is high, combined pH-impedance on PPI should be the preferred method as the main question now focuses on why the medicine is not working.

III. Diagnostic and treatment algorithm for PPI non-responders

The real management issue in current practice is focused on dealing with refractory symptoms in patients who are on optimized PPI therapy with a negative endoscopy. A more accurate definition of this clinical dilemma should focus on the lack of response to therapy and thus, “PPI non-responder” is an appropriate term. The mechanism behind PPI non-response may be related to non-reflux pathophysiology or to refractory gastroesophageal reflux and therefore, the latter is actually a sub-category of PPI non-response causes.

The evaluation of patients that are not responding to PPI therapy begins by first documenting that the patient is compliant with medical management (Figure 1b). A recent systematic review of PPI adherence in GERD found that ~40–50% of patients on PPI therapy are not compliant with their medication.[22] In addition to daily compliance, less than 50% of patients take their PPI optimally (timing, frequency, and dose).[23] Most of the current guidelines support empiric treatment with FDA-approved single dose PPI therapy for a 4–8 week period for a patient presenting with typical GERD symptoms.[8] Patients should also be taking their medications 30–60min before meals for optimal acid suppression, although this can be liberalized if the patient is taking formulations such as dexlansoprazole or omeprazole sodium-bicarbonate.[24,25] If the patient fails single dose therapy, it is reasonable to escalate therapy to double dose as there is little risk to this practice and a small group of patients may respond.

One caveat to empiric treatment focuses on the presence or absence of warning signs. Although there is controversy regarding the predictive value of warning symptoms, an upfront endoscopy is reasonable if there is evidence of dysphagia, odynophagia, GI bleeding, unintentional weight loss, early satiety or age at presentation greater than 55 to rule out significant complications and malignancy.[12] In the absence of warning signs, patients are typically not referred for endoscopy unless they have failed a course of optimized PPI therapy. The timing of endoscopy in the algorithm and the dose of PPI that is considered a failure which warrants endoscopic evaluation is unclear, however, we would recommend a trial of double dose therapy.

As mentioned above, patients who fail initial single-dose FDA-approved PPI therapy will have their acid suppression therapy increased to at least double the FDA-approved dose.[9] The data to support the yield of an escalation of PPI therapy to double dose in patients not responding to single dose is marginal and likely in the range of 10–20%.[26] Once patients are documented to have a poor or inadequate response to optimize PPI therapy (double dose PPI), the next most important steps are a) to document whether or not the patients actually have abnormal gastro-esophageal reflux and b) to document whether or not their symptoms experienced on medication are associated with reflux. Other diagnoses should also be considered including gastroparesis which can contribute to refractory reflux symptoms.

Updated comprehensive clinical guidelines have been recently published regarding the diagnosis and management of gastroparesis.[27] By focusing on these specific issues, further physiologic testing can distinguish four specific phenotypes of PPI non-responders. The four specific phenotypes of PPI non-responders are described in Table 1.

The first distinction in the phenotypes is focused on determining whether or not the patient has baseline abnormal gastro-esophageal reflux (Figure 1c). Phenotypes 1 through 3 are patients who have abnormal gastro-esophageal reflux off PPI therapy, but continued to have symptoms that are either partially treated or secondary complaints that may (Phenotypes 1 & 2) or may not (Phenotype 3) be related to reflux. Phenotypes 1 and 2 have continued symptoms that are related to reflux and these subtypes are truly refractory GERD. Phenotype 1 will have evidence of abnormal acid exposure on ambulatory pH reflux testing and/or a positive symptom reflux correlation in the context of overt abnormal acid exposure or normal acid exposure associated with an acid hypersensitivity. Similarly, phenotype 2 will also have a positive symptom reflux correlation; however, the correlation is not associated with overt abnormality in distal esophageal acid exposure and these patients are likely hypersensitive to a) volume, b) other components of the gastric refluxate or c) refluxate with a pH above 4. These particular phenotypes may respond to an escalation of anti-reflux therapy focused on reducing acid burden and the overall number of reflux events. Alternative options for therapy include baclofen, which has been shown to reduce transient lower esophageal sphincter relaxation[28], although evidence from studies to date has involved small numbers of patients.[29,30] Surgical therapy (fundoplication) may also be discussed with the patient and local surgical team, including minimally invasive approaches which have shown some promise.[31] Prokinetic agents are sometimes attempted but when previously compared to PPI therapy, cisapride was found to be no more effective than placebo[32] and significantly less effective than omeprazole.[33] A systematic Cochrane review found no recent quality placebo controlled trials evaluating the efficacy of prokinetics for endoscopy negative reflux disease.[34] In addition, a recent randomized controlled trial evaluating the addition of mosapride to omeprazole showed no benefit over omeprazole alone in NERD.[35]

Phenotypes 3 and 4 are important to distinguish from phenotypes 1 and 2 because they should exhibit a lack of response to more aggressive anti-reflux therapy. However, phenotype 3 patients do have baseline reflux disease and many require PPI therapy to maintain control of other symptoms that are related to abnormal reflux. This particular group of patients will exhibit pathologic acid reflux off PPI therapy and normalization on PPI therapy with a negative symptom correlation with all types of reflux events. Ambulatory reflux testing on PPI therapy incorporating impedance may reveal an increased number of overall reflux events suggesting underlying baseline GERD. Thus, these patients will be unable to discontinue PPI therapy and will require an evaluation for alternative causes and therapy beyond reflux suppression. In contrast, phenotype 4 patients will have no evidence of abnormal reflux or a symptom-reflux correlation at baseline or on PPI therapy. This group of patients can be labeled as functional heartburn once an endoscopy has ruled out alternative causes and manometry has not revealed an underlying esophageal motor disorder. These patients should have their PPI therapy discontinued and will likely require therapy focused beyond acid suppression and reflux inhibition.

Evidence to support this phenotypic classification can be found in recent studies assessing large series of referral patients for combined pH-impedance testing both off and on PPI therapy. Savarino *et al.* noted in a series of 200 patients with non-erosive reflux disease that 27% had normal esophageal acid exposure and negative symptom association probability on 24-h pH-impedance monitoring performed off PPI (phenotype 4).[36] Eleven percent of the patients presented with a positive association between symptoms and non-acid reflux events

only in the absence of PPI therapy. Mainie *et al.* also observed different phenotypes of PPI non- responders in a series of 168 patients who underwent 24-h pH-impedance monitoring on PPI for refractory GERD symptoms.[37] Eleven percent of subjects had a persistent pathological esophageal acid exposure despite PPI twice daily (phenotype 1), 31% had a positive association between symptoms and non-acid reflux (phenotype 2) and 58% had no evidence of pathological reflux and/or positive association on PPI (phenotypes 3 and 4). As data on esophageal pH monitoring off PPI were not available for these patients it is not possible to differentiate phenotypes 3 and 4.

IV. Should PPI therapy be stopped based on ambulatory reflux testing results?

The treatment of refractory reflux symptoms remains challenging and identification of PPI non-responders phenotypes may provide the pathophysiological basis to help guide therapy. Improving reflux inhibition may be proposed in patients with phenotypes 1 and 2, whereas treatment strategies targeting visceral hypersensitivity may be more relevant in phenotypes 3 and 4. In these patients, it would be reasonable to recommend decreasing or stopping therapy. This is easier said than done in clinical practice as we recently found that up ~42% of patients with negative results from reflux tests continued PPI therapy and very few were ever told to attempt to stop therapy.[10] Proton pump inhibitors are often the last line of therapy provided to patients with refractory symptoms and due to widespread availability are difficult to stop in many patients. There is also very limited research on effective interventions to stop prescribing of unwarranted medications, including PPIs.[38] The American Gastroenterological Association and American Board of Internal Medicine have taken one step by highlighting PPI use in the widely publicized “Choosing Wisely” campaign which states that if empiric or escalated PPI dosing does not control GERD symptoms within the recommended 4–8 weeks, the medication should be stopped and alternative options assessed.[39] However, the effects of this campaign on prescribing habits and patient behavior are not yet known and the campaign also does not specifically address the use of ambulatory reflux monitoring to guide clinical decision making.

Another dilemma is long term continuation of therapy in patients with symptom response but normal ambulatory reflux testing. The individual risk of PPI use is small but there is data linking PPIs to a higher risk of fracture, Pneumonia, and *Clostridium difficile* diarrhea.[40–42] Although the absolute risks of these conditions is small for individual patients, due to the large number of PPI prescriptions it is estimated that >30,000 patients could be harmed annually by one of these conditions.[43] Recently, the FDA announced a safety alert for PPI use and associated risk of *C. Diff* infection.[44] In their review of 28 observational studies, 23 showed that patients treated with PPIs had a 1.4 to 2.75 times higher risk of *C difficile* infection or disease.[44] Although the strength of these associations is variable and the overall safety profile remains good, efforts should be made to decrease unnecessary long term PPI use in the general population, especially in those patients without any objective evidence (i.e. positive ambulatory reflux monitoring results) of reflux disease.

In the case of persistent symptoms despite active PPI treatment and negative ambulatory reflux testing, systematic efforts should be made to evaluate other potential causes of symptoms and alternative approaches to therapy.[21] As stated above, select patients may respond to baclofen[29,30] There is also modest evidence that anti-depressants (e.g. tricyclic anti-depressants, selective serotonin reuptake inhibitors) can modulate pain, especially non-cardiac chest pain, although rigorous trials and definitive evidence is lacking.[45]

Non-pharmaceutical therapies are also an option. There has been promising recent research showing that abdominal breathing exercises can improve GERD symptoms.[46] Our group has

also shown a benefit of hypnotically assisted relaxation therapy for globus sensation[47], and work is ongoing to evaluate if similar results can be obtained in patients with functional heartburn. Overall, therapeutic options are still limited and further studies are required to evaluate and provide evidence for alternative treatment strategies that could replace or augment PPI therapy.

CONCLUSION

Reflux testing is important in documenting the primary pathophysiologic outcome responsible for GERD and thus, is an important component of the current management strategy. Symptoms, empiric PPI therapy, and endoscopy play a role but are often not sufficient for making a diagnosis of GERD or other syndromes (i.e. functional heartburn). Ambulatory reflux monitoring, when used appropriately, is useful in distinguishing etiologies driving a lack of response to PPI therapy. Reflux testing results can be used to guide appropriate PPI prescribing and clinical decision making for appropriate or unnecessary therapy. The question of whether or not to stop therapy in PPI non-responders should be supplemented by objective evidence of the likelihood of true reflux disease. Ambulatory reflux monitoring provides valuable information to help physicians and patients choose therapeutic options, and perhaps even more importantly, stop unnecessary therapy. Therapeutic options for PPI non-responders are limited and alternative therapies should be sought and investigated in larger, well designed randomized controlled trials. Future work is also needed to determine the most efficient approach to diagnostic testing to avoid inappropriate long term PPI therapy and overuse of endoscopy.

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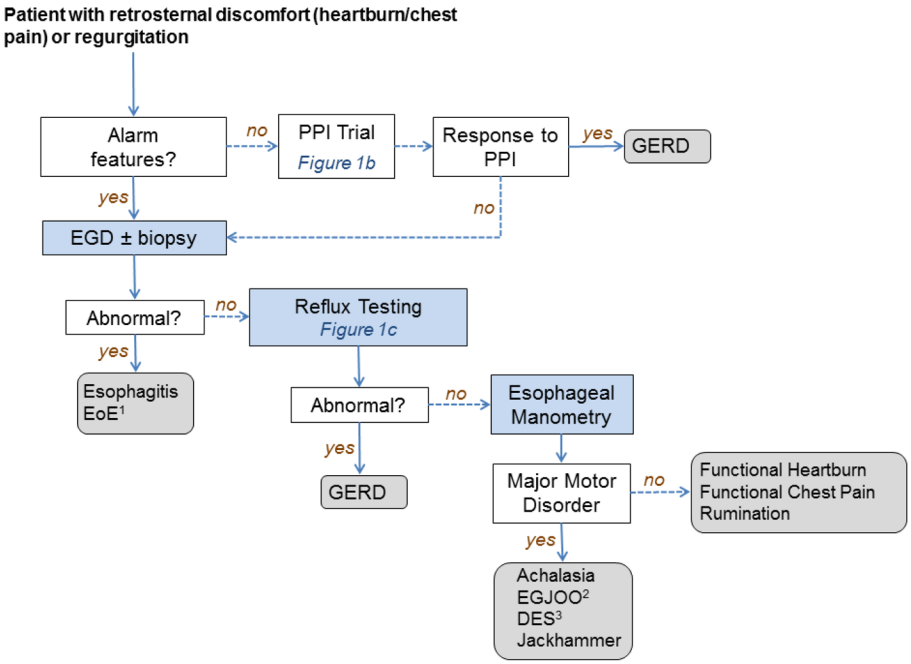

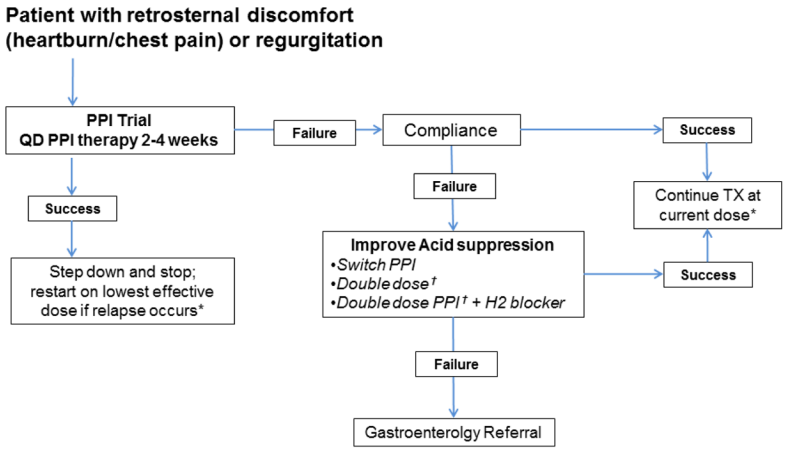

*Consider endoscopy for patients requiring chronic therapy if BE is a concern
† Not FDA approved

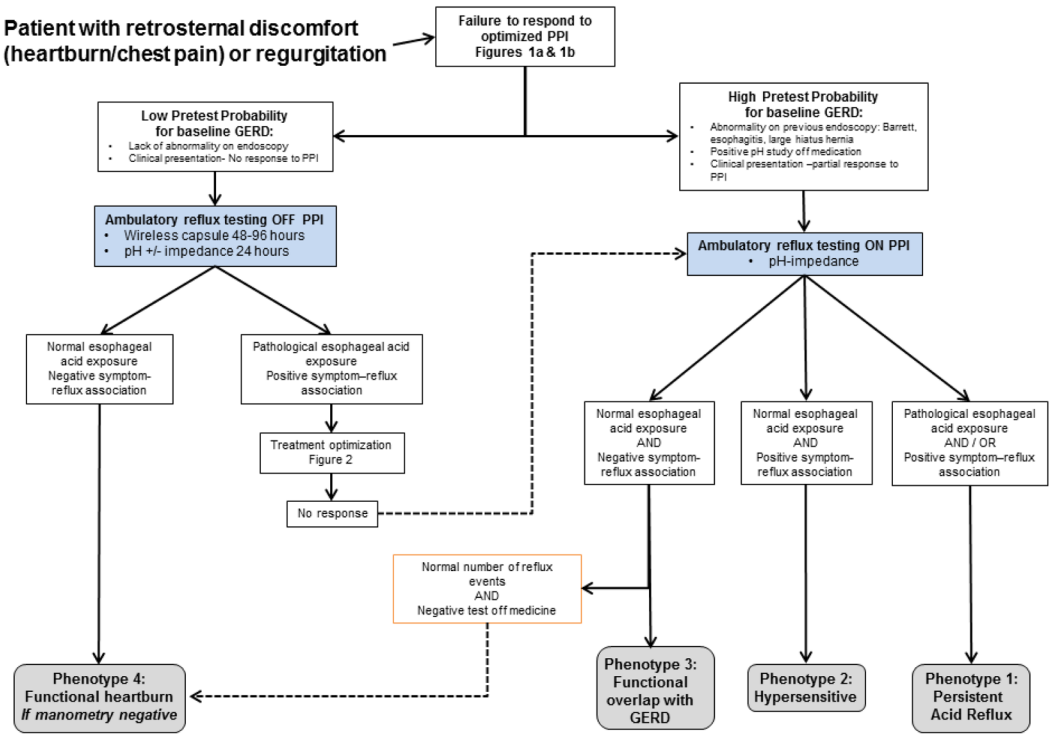

Figure 1.

Figure 1a: Diagnostic approach for patients presenting with reflux symptoms (modified from Kahrilas and Smout[2]) [1] EOE=eosinophilic esophagitis; [2] EGJOO=esophagogastric junction outflow obstruction; [3] DES=diffuse esophageal spasm

Figure 1b: Empiric proton pump inhibitor therapy for patients with reflux symptoms (modified from Tytgat et al.[9])

Figure 1c: Ambulatory reflux monitoring algorithm for PPI non-responders (modified from Richter et al.[48])

Table 1

Phenotypes of PPI non-responders based on physiologic testing

	Phenotype 1	Phenotype 2	Phenotype 3	Phenotype 4
	Persistent acid reflux	**Hypersensitive**	**Functional overlap with GERD**	**Functional heartburn**
Acid esophageal exposure ***off*** PPI *	+	+/−	+	−
Acid esophageal exposure ***on*** PPI *	+	−	−	−
Excessive number of reflux events with impedance ***on*** PPI	+/−	+/−	+	−
Positive reflux- symptom association with impedance ***on*** PPI	+/−	+	−	−

* prolonged wireless pH monitoring both off and on PPI may be used to evaluate esophageal acid exposure in a single examination [8]