The Spectrum of Reflux Phenotypes

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Abstract: The focus on a symptom-based definition for gastroesophageal reflux disease (GERD) in adults and children has contributed to widespread use of acid suppression medications in patients with so-called typical reflux symptoms to treat the possibility of acid-mediated disease. Diagnostic testing with upper endoscopy, esophageal biopsies, ambulatory reflux monitoring, and/or esophageal manometry is often pursued when patients do not respond optimally to these medications. By using information from this diagnostic testing, GERD has shifted from a single diagnosis to a phenotypic spectrum, and each phenotype has unique pathophysiologic mechanisms driving symptom perception. Understanding these mechanisms is important to tailor individualized treatment plans and guide therapeutic interventions. The aim of this article is to discuss the different reflux phenotypes, the utility of esophageal reflux testing, the mechanisms underlying symptoms, and the management strategies for each phenotype.

Gastroesophageal reflux disease (GERD) is one of the most common disorders encountered in outpatient gastroenterology practices. With up to 15% of adults and 10% of children reporting symptoms of gastroesophageal reflux on at least a weekly basis, heartburn is the most commonly reported gastrointestinal (GI) symptom, and GERD accounts for 5.6 million office visits annually in the United States.[1-3] In 2006, the Montreal consensus formalized the definition of GERD in adults as "a condition that develops when the reflux of stomach contents into the esophagus causes troublesome symptoms and/or complications."[4] Pediatric consensus guidelines adopted a similar definition.[5] With the focus on subjective symptom-based definitions, there was widespread use of empiric acid suppression medications in symptomatic patients to treat the possibility of acid-mediated symptoms. However, in the years that followed, a subpopulation of patients emerged who had so-called typical reflux symptoms but who did not respond to acid suppression, suggesting that acid alone may not be wholly responsible for their reflux symptoms. Refractory symptoms despite acid suppression prompted the performance of additional diagnostic studies, shedding light on the role of other factors contributing to symptom perception, such as weakly acidic reflux, esophageal hypersensitivity, motility disorders, and functional disorders. As a result, GERD became a more heterogeneous disorder, a concept that was highlighted in the 2016 Rome IV classification of functional esophageal disorders.[6]

Recognizing that many patients with typical reflux symptoms who undergo endoscopic evaluation do not have erosive reflux disease, this classification delineated different nonerosive reflux disease (NERD) phenotypes based on the results of esophageal reflux testing with multichannel intraluminal impedance (pH-MII): (1) true NERD (abnormal esophageal acid exposure), (2) reflux hypersensitivity (normal esophageal acid exposure and positive symptom correlation), and (3) functional heartburn (normal esophageal acid exposure and negative symptom correlation). The current conceptualization of GERD in both adults and children is now one of a phenotypic spectrum, rather than a single diagnosis, with a complex interplay between physiology, hypersensitivity, and psychological factors driving symptom perception. The objective of this article is to discuss the spectrum of phenotypes in patients with typical reflux symptoms.

Defining What Constitutes Typical Reflux Symptoms

Heartburn and regurgitation are the most commonly reported symptoms of reflux in adults and have traditionally been considered typical GERD symptoms. However, there is not always correlation between the presence of typical symptoms and objective measures of reflux. In a randomized, placebo-controlled trial of 14 days of esomeprazole vs placebo in symptomatic patients, less than half of patients with abnormal reflux testing reported heartburn or regurgitation as their most troubling symptom.[7] Similarly, in a study of 62 adults with proton pump inhibitor (PPI)-refractory symptoms undergoing endoscopy and pH-MII testing, Kandulski and colleagues found no differences in the frequency of reported heartburn or regurgitation in patients with erosive reflux disease, NERD, or functional heartburn.[8] Similar results were reported by Savarino and colleagues, in which the frequency of reported heartburn and regurgitation differed little among patients with NERD, reflux hypersensitivity, and functional heartburn.[9]

The pediatric reflux guidelines differentiate physiologic gastroesophageal reflux from pathologic GERD based on the presence of troublesome symptoms and/or complications.[5,10] However, this symptom-based diagnosis is complicated by the fact that it is often the parents, rather than the patients, reporting that the symptoms are troublesome. Furthermore, the typical symptoms of reflux in children are less well defined and can vary significantly by age. Children are most likely to report regurgitation, abdominal pain, and cough as symptoms of reflux, regardless of whether they have erosive or nonerosive disease.[11] Younger children also commonly report feeding refusal. In a survey of children with reflux symptoms and their parents, Nelson and colleagues found that stomachache was the most commonly reported symptom of GERD in all ages, with far fewer children reporting heartburn or regurgitation.[12] In contrast to findings in adult studies, symptom reports may vary by phenotype in children; children with NERD report higher rates of regurgitation and those with functional disorders are more likely to report nonspecific abdominal pain.[13]

Diagnostic Testing for Reflux

Proton Pump Inhibitor Trial

In patients reporting typical reflux symptoms, PPIs are commonly used as a diagnostic test to determine whether the symptoms are mediated by acid, although studies suggest that this test may lack the sensitivity and specificity needed for diagnosis. In a secondary analysis of data from the prospective multinational DIAMOND study of patients presenting with reflux symptoms in a primary care setting, Bytzer and colleagues found that a PPI trial had poor sensitivity and specificity in detecting GERD, with a positive response to the trial in 69% of patients with GERD and in 51% of individuals without GERD.[14] In a meta-analysis, Numans and colleagues also found that a short-term PPI test had poor sensitivity and specificity in detecting GERD when using an abnormal 24-hour pH study or esophagitis on endoscopy as references.[15] Finally, in a prospective study of patients with a favorable response to a PPI who then underwent pH-MII testing off therapy, de Bortoli and colleagues found that only 55% had pathologic esophageal acid exposure, and the remaining patients had reflux hypersensitivity or functional heartburn.[16] The utility of the PPI trial is further limited by a lack of clear guidelines for dosing, frequency, and duration, and by genetic differences in PPI metabolism.[15,17]

Endoscopy

Upper endoscopy is commonly performed in symptomatic patients when reflux is suspected. The role of endoscopic evaluation is to assess the mucosa in the presence of alarm symptoms, detect complications from GERD, diagnose erosive and microscopic esophagitis, and diagnose other mucosal disorders that may mimic GERD. The majority of patients with refractory symptoms have grossly normal endoscopic evaluations; only 30% of adults with refractory symptoms studied off acid suppression have erosive esophagitis.[18,19] The prevalence of erosive esophagitis is even lower in children compared to adults.[20,21] Microscopic esophagitis may aid in the diagnosis of GERD, although this finding is not sensitive or specific enough in isolation, as microscopic esophagitis can be present in up to 15% of asymptomatic healthy controls.[8,22,23] In addition to diagnosing microscopic esophagitis, biopsies

are helpful in ruling out non-GERD conditions such as eosinophilic esophagitis (EoE).

Ambulatory Reflux Monitoring

Twenty-four–hour pH or pH-MII testing is often done in patients with refractory symptoms despite PPI therapy. pH-MII testing is often considered the gold standard in diagnosing GERD, as it offers the ability to determine the total reflux burden, detects both acid and nonacid reflux, measures the esophageal acid exposure time, and assesses the correlation between symptoms and acid or nonacid reflux events. Nonacid reflux, which can only be detected when impedance testing is added to pH monitoring, has been shown to be a major driver of symptoms in both children and adults.[24,25] Wireless pH monitoring, placed endoscopically, is also available in patients unable to tolerate a transnasal catheter, when nonacid reflux is not a concern, or if monitoring longer than 24 hours is clinically indicated.[26] Reference ranges have been established for some pH-MII parameters. Esophageal acid exposure is generally considered abnormal when the pH is less than 4 for more than 6% of the study duration in adults and older children tested off therapy,[26] although values as high as 12% have been reported in healthy asymptomatic neonates.[27] Cutoffs are lower in patients tested on PPI therapy, ranging from 0.4% to 4.0% based on the study.[28,29] The criteria for an abnormal reflux burden are less clearly defined. The upper limit of normal for the number of reflux episodes detected by impedance is often reported to be 73 in many studies, although it can range from 57 to more than 100 based on the study and patient age.[27,28,30] While the total reflux burden can be a piece to the puzzle when assessing a patient's symptoms, little data exist linking it to patient outcomes.[31]

Measures of Symptom Association

Differentiating between reflux hypersensitivity and functional heartburn requires the ability to accurately measure symptom-reflux association during 24-hour reflux monitoring. There are 3 measures of symptom association used in the interpretation of pH-MII studies: (1) the symptom index (SI) is calculated by dividing the number of reported symptoms associated with reflux by the total number of reported symptoms and multiplying by 100 (positive SI ≥50%)[26,29]; (2) the symptom sensitivity index (SSI) is the number of reflux events associated with symptoms divided by the total number of reflux events over 24 hours, multiplied by 100 (positive SSI ≥10%)[32]; and (3) the symptom association probability (SAP) is calculated by computing the statistical association between symptoms and reflux events using the Fisher's exact test (positive SAP ≥95%).[26,29]

Despite their widespread use, there are limitations to these indices. First, measures of symptom association rely on a patient's ability to accurately report symptoms by pressing the event monitor. However, patient-reported symptoms have been shown to have poor accuracy when compared to objective assessment.[33] Furthermore, symptom reporting is often challenging in younger children, who are unable to self-report symptoms. Second, there are very little outcome data to validate the utility of these measurements in differentiating reflux hypersensitivity from functional heartburn, and the results are mixed. While some authors have found the SAP to have predictive value for symptomatic improvement,[34] others have found very few differences in reflux or symptom parameters in SAP-positive and -negative patients.[35] Third, there is daily variation in the measures of symptom association, which may further limit the ability to interpret findings in a clinically meaningful way and could impact phenotypic classifications.[35-37] Finally, in patients who do not have a large number of reflux episodes or who only report a few symptoms during the study, the indices can be positive due to chance alone.[36]

Esophageal Manometry

Esophageal manometry is commonly used in the diagnostic evaluation of reflux symptoms in adults, where it aids in the proper placement of pH or pH-MII catheters, assesses esophageal body peristaltic performance, describes the esophagogastric junction morphology, and rules out non-GERD motility disorders.[29,38] While there is no evidence to support the routine use of esophageal manometry in children with reflux symptoms, it may be helpful in assessing for R waves and retrograde bolus flow seen with rumination disorder, which may mimic refractory reflux symptoms.[10]

Diagnostic Testing on or off Proton Pump Inhibitors

Diagnostic testing to evaluate for reflux is often performed when a patient has persistent bothersome symptoms despite a trial of acid suppression, although recently there has been a trend to test even before empiric therapy. Up to 32% of adults in randomized trials and 45% of patients in observational studies have refractory heartburn and/or regurgitation despite PPIs.[39] Refractory symptoms could be related to medication compliance or dosing, presence of nonacid or bile acid reflux, differences in PPI metabolism due to genetic polymorphisms in CYP2C19, other esophageal mucosal diseases, esophageal motility disorders, visceral hypersensitivity, and brain-gut factors.[40-44] As a result of this complexity, the pendulum is swinging toward consideration of diagnostic testing prior to empiric treatment to accurately detect erosive reflux disease or PPI-responsive EoE, as pretreatment will result in a falsely

normal endoscopy.[45] For example, in a prospective cohort study, Gaddam and colleagues found that 10% of patients ultimately diagnosed with NERD actually had erosive reflux disease that was misclassified due to PPI use.[46]

The decision of whether to perform ambulatory reflux testing on or off PPI therapy depends on the information desired by the clinician and the pretest probability of GERD. In patients with typical symptoms who have not responded to acid suppression therapy, testing off PPIs allows clinicians to determine the presence of reflux, the native esophageal acid exposure, and whether these factors are a cause for the symptoms. Testing on PPI therapy is useful when trying to assess whether suboptimal response to medical therapy is due to incomplete acid suppression or when monitoring response to therapy in individuals with a history of pathologic GERD.[6,26]

Defining Reflux Phenotypes Based on Esophageal Reflux Testing

The majority of patients with persistent reflux symptoms who undergo upper endoscopy have normal studies. These patients were traditionally grouped together as a single entity of NERD in contrast to erosive reflux disease. However, the most recent version of the Rome IV criteria for functional esophageal disorders highlighted this heterogeneous group as a spectrum with varying degrees of esophageal acid exposure and esophageal hypersensitivity based on the results of diagnostic testing with upper endoscopy and pH-MII.[6] As a result, several distinct phenotypes can be defined based on the results of this diagnostic testing: true NERD (abnormal esophageal acid exposure), reflux hypersensitivity (normal esophageal acid exposure and a positive symptom-reflux association with either acid or nonacid reflux), and functional heartburn (normal esophageal acid exposure and a negative symptom-reflux association), as outlined previously. While NERD is the most prevalent phenotype in adults, the majority of children can be classified as having the functional heartburn phenotype.[13,19,47]

Mechanisms of Reflux Hypersensitivity and Functional Heartburn

The mechanisms underlying symptoms in reflux hypersensitivity and functional heartburn, where acid is less likely to play a role, are multifactorial. Proposed mechanisms include the quality of reflux episodes, impaired mucosal integrity, central and peripheral sensitization, and psychological factors.

Esophageal hypersensitivity may be related to the quality of the reflux episodes. Studies have shown that full column reflux, mixed liquid-gas reflux episodes, weakly acidic reflux, and impaired chemical clearance can all trigger symptoms in patients with reflux hypersensitivity.[48-51] Patients with esophageal hypersensitivity may also have altered mucosal integrity. A variety of histologic abnormalities have been reported in patients with reflux hypersensitivity, including basal cell hyperplasia, papillary elongation, inflammatory cell infiltration, and dilated intercellular spaces, although these have not consistently been shown to correlate with symptom severity.[8,52,53] Higher rates of microscopic esophagitis have been reported in patients with reflux hypersensitivity when compared to controls or patients with functional heartburn, although individuals with functional heartburn have rates similar to those of healthy volunteers.[23,54]

There is also likely some component of central and peripheral pain sensitization. In a recent study examining the distribution of nociceptive sensory mucosal nerve fibers in patients with NERD, erosive reflux disease, and Barrett esophagus and in controls, Woodland and colleagues found significantly more superficial proximal and distal esophageal afferent nerves in patients with NERD compared to the other groups.[55] In contrast, in patients with functional heartburn, the distribution of afferent nerve fibers in the distal esophagus was similar to that of healthy asymptomatic controls, and both groups had significantly deeper nerve fibers compared to patients with NERD.[56] Visceral hypersensitivity also likely plays a role in symptom perception in patients with functional heartburn, who have significantly higher mechanosensitivity to balloon distention and chemosensitivity to acid perfusion, when compared to either healthy controls or patients with NERD.[57] A number of pain-related genetic risk factors and molecular biomarkers have also been reported to be associated with increased symptom perception, with variation in G-protein beta-3 subunit, transient receptor potential channel vanilloid subfamily member-1, protease-activated receptor 2, substance P, and calcitonin gene–related peptide implicated in esophageal hypersensitivity.[58-61]

Finally, there is also a role for brain-gut interplay in symptom perception. Functional heartburn has been associated with other functional GI disorders, suggesting that there may be a predisposition to pain syndromes.[62] Psychological and physiologic stress has also been found to modulate pain perception to esophageal stimuli.[63-65] This symptom burden in patients with functional heartburn is associated with significant psychosocial distress, impaired quality of life (QOL), anxiety, and depression.[66-68]

Why the Diagnosis Matters for Management

Acid Suppression

From a pathophysiologic perspective, PPIs have the most benefit when patients have acid-mediated symptoms or

complications such as erosive esophagitis, where healing rates as high as 95% have been reported within 8 weeks of starting PPI therapy.[69] Patients with true NERD (defined as a negative endoscopy and positive pH measurement) have similar rates of response to 4 weeks of PPI treatment as patients with erosive reflux disease.[70] Children and adolescents with NERD also report significant improvement in heartburn, better QOL, and less rescue medication use after a 4-week PPI trial.[71] Rates of symptom improvement with PPIs are less impressive in patients without pathologic acid. Patients with reflux hypersensitivity and functional heartburn have lower rates of PPI responsiveness when compared to patients with NERD.[16]

Histamine 2 receptor antagonists (H2RAs) may also be helpful in managing esophageal hypersensitivity. Marrero and colleagues randomized 27 symptomatic patients with a negative endoscopy and an abnormal 24-hour pH study to receive either 40 mg of famotidine or placebo daily for 4 weeks.[72] The investigators found significant increases in time to induce heartburn on esophageal acid perfusion tests compared to baseline in the famotidine group compared to the placebo group, suggesting that there may be a role for the medication in modulating acid-related hypersensitivity even when esophagitis is not present. This effect may also be seen even in the absence of pathologic acid. Similar results were shown in a randomized, placebo-controlled, crossover study of patients with functional heartburn receiving 7 days of once-daily oral ranitidine vs placebo who underwent balloon distention and acid infusion studies.[73] Ranitidine significantly reduced esophageal sensitivity to acid on testing done on days 1 and 7, although the drug did not have any impact on balloon distention sensory parameters. The authors hypothesized that symptomatic improvement with ranitidine is due to modulation of the esophageal pain receptors rather than mucosal healing, although further research is needed in this area to understand the underlying mechanisms. Long-term use of H2RAs has been associated with tachyphylaxis, and this should also be considered in the management of patients with esophageal hypersensitivity.

While acid suppression medications have a role in the management of NERD and acid reflux hypersensitivity, many patients remain on acid suppression long term despite no evidence of pathologic acid on diagnostic testing. Gawron and colleagues conducted a follow-up survey of 90 patients with negative Bravo, pH, or pH-MII testing, and found that 42% of patients remained on a PPI at follow-up despite negative testing.[74] Given the mounting concern regarding the potential risks associated with long-term PPI use, acid suppression medications should be discontinued when diagnostic testing does not support acid-mediated symptoms.

Antireflux Surgery

Fundoplication has been shown to significantly improve outcomes in patients with NERD. In a long-term outcome study in patients with PPI-refractory symptoms and pathologic acid exposure, Broeders and colleagues showed significant improvement in symptoms and QOL 5 years after fundoplication in a cohort of patients with and without a positive SAP.[75] A recent retrospective cohort study found that approximately two-thirds of patients with NERD who underwent fundoplication had no recurrence of heartburn or regurgitation when followed for over 5 years.[76] However, even patients without an abnormal esophageal acid exposure may benefit from antireflux surgery. In a prospective cohort study, Patel and colleagues found that patients with reflux hypersensitivity may have greater symptom improvement with surgical vs medical therapy.[77] In another study, Broeders and colleagues also showed significant improvement in QOL, reduced PPI use, lower acid exposure time, decreased esophagitis, and improved symptoms 3 months after fundoplication in 28 patients with acid reflux hypersensitivity refractory to PPIs.[78] Patients with nonacid reflux hypersensitivity may also benefit from antireflux surgery.[79,80]

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have been studied in a variety of reflux phenotypes. Viazis and colleagues randomized 75 patients with reflux hypersensitivity to receive either 20 mg of citalopram daily or placebo for 6 months.[81] At the end of the study, 62% of the patients randomized to the citalopram arm were symptom free vs 33% in the placebo arm.[81] In a randomized, crossover, double-blind study of 10 patients with reflux hypersensitivity undergoing esophageal manometry, Broekaert and colleagues found that patients receiving citalopram required greater balloon volumes to induce initial perception and discomfort compared to patients receiving placebo.[82] Patients receiving citalopram also required longer esophageal acid perfusion time to induce initial perception and discomfort. SSRIs may also be beneficial in patients with functional heartburn. Ostovaneh and colleagues randomized PPI nonresponders with functional heartburn to 20 mg of omeprazole daily, 20 mg of fluoxetine daily, or placebo for 6 weeks.[83] Patients randomized to fluoxetine had greater improvement in the percentage of heartburn-free days than patients on either omeprazole or placebo.

Tricyclic Antidepressants

Tricyclic antidepressants have been successfully used in the management of functional esophageal disorders such as noncardiac chest pain, although few studies have evaluated their use in reflux phenotypes.[84] In a randomized,

double-blind, crossover study of patients with heartburn and normal endoscopy off PPI therapy, Forcelini and colleagues randomized patients to receive 21 days of nortriptyline and placebo with a 21-day washout period, and assessed acid-induced brain response on functional magnetic resonance imaging.[85] While nortriptyline decreased the brain response to esophageal acid perfusion when compared to placebo, there were no differences between the groups with regard to symptom report or QOL scores. Limsrivilai and colleagues randomized PPI nonresponders with pH-MII–defined reflux hypersensitivity or functional heartburn to 8 weeks of imipramine vs placebo.[86] There were no significant differences between the groups for the primary endpoint of satisfactory relief of reflux symptoms in either phenotype, although imipramine treatment was associated with improved QOL scores.[86]

Other Medications

A number of other medications have been proposed in the management of symptoms in NERD in general, although none have been specifically evaluated when using the more recent definitions for reflux phenotypes. Patients with NERD receiving alginates in combination with PPIs were more likely to have complete resolution of heartburn compared to omeprazole alone.[87,88] Baclofen inhibits transient lower esophageal sphincter relaxations and reduces acid and nonacid reflux episodes and symptoms in both adults and children with reflux symptoms, but its use is limited by the unfavorable side-effect profile.[89-91] Prokinetics have also been studied for NERD, although in a meta-analysis, the addition of prokinetics to PPIs was not associated with significant symptom improvement, reduction in acid exposure time, or endoscopic response.[92] The use of alginates, baclofen, or prokinetics is not recommended in the management of reflux symptoms in children.[10]

Complementary Therapies

Complementary therapies are often recommended in the management of patients with refractory heartburn, particularly those with functional heartburn, although robust data in this area are lacking. There are some limited data to suggest that melatonin may be helpful in reducing heartburn symptoms in patients with functional heartburn when compared to nortriptyline or placebo.[93] In small studies in patients with functional heartburn, esophageal-directed hypnotherapy, acupuncture, and deep breathing have been shown to reduce heartburn and esophageal hypersensitivity, although biofeedback was less helpful.[94-97] There are also some data on using cognitive behavioral therapy (CBT) in the management of patients with functional esophageal disorders. Li and colleagues studied 115 patients with NERD (diagnosed only based on endoscopy) and mood disorders randomized to receive drug (omeprazole and domperidone) alone, CBT alone, or drug plus CBT.[98] Patients receiving any CBT had more significant decreases in depression, anxiety, and QOL measures compared to patients not receiving CBT. CBT has also been shown to be helpful in reducing esophageal acid exposure time and improving QOL in patients with supragastric belching.[99]

A variety of diagnostic algorithms have been proposed for the evaluation and management of adults with bothersome reflux symptoms,[6,26,29,84] although few exist for children.[10] A proposed algorithm for the approach to older children with bothersome symptoms is shown in the Figure.

Conclusion

Studying patients with typical reflux symptoms in the PPI era has shed light on the complexity of a GERD diagnosis. With recent advances in diagnostic testing, GERD has shifted from a single diagnosis to a spectrum of phenotypes, each of which has its own underlying pathophysiologic mechanisms. Esophageal reflux testing has enabled clinicians to define, characterize, and study these phenotypes. The therapeutic approach to patients with reflux symptoms has shifted away from acid suppression for all patients to individualized therapies targeting the unique mechanism for each patient. Prospective studies in both children and adults are needed to better clarify the prevalence of these phenotypes, identify specific risk factors, and guide the optimal personalized management plan for each patient.

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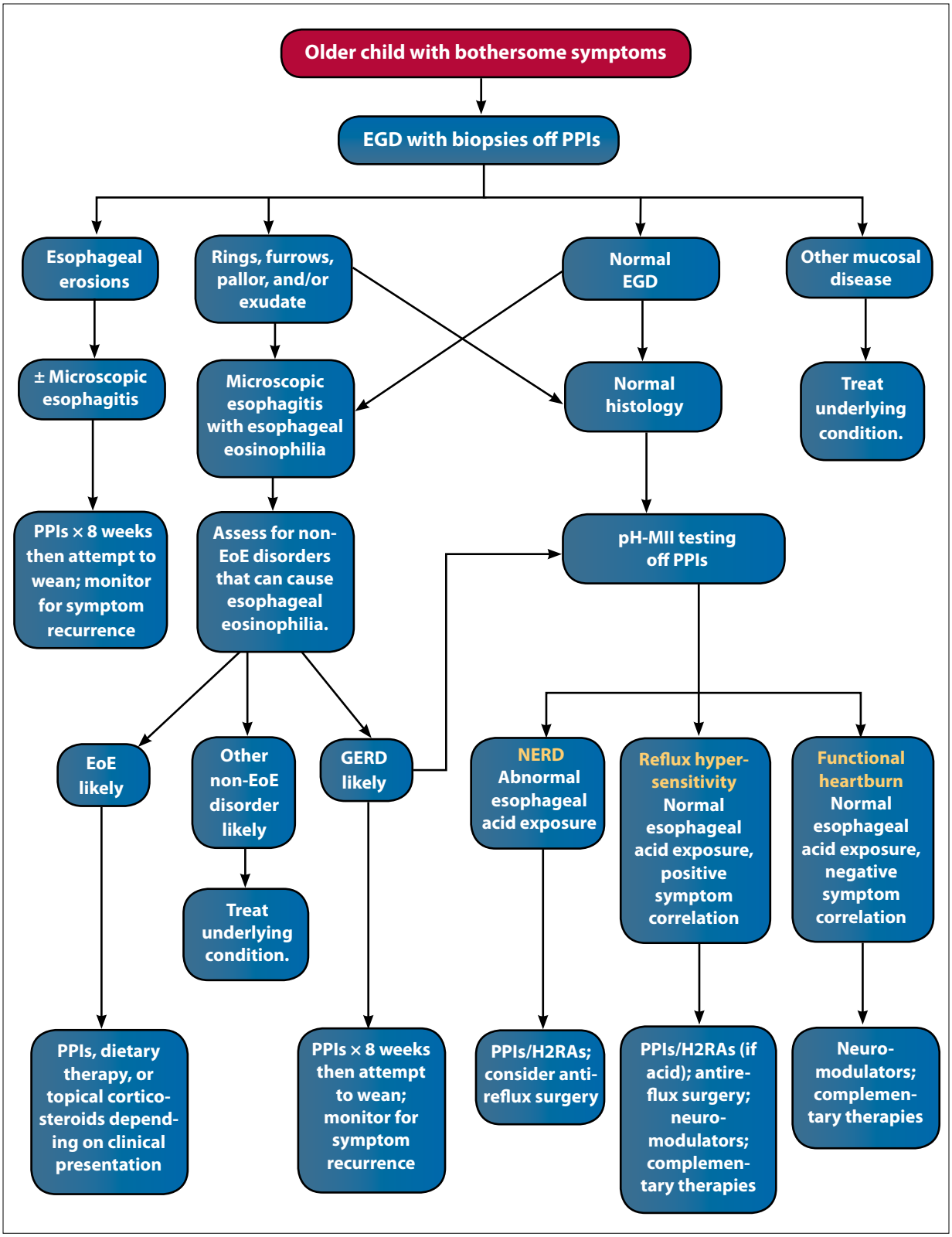

Figure. Proposed algorithm for the approach to bothersome symptoms in older children.

EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; H2RA, histamine 2 receptor antagonist; NERD, nonerosive reflux disease; pH-MII, multichannel intraluminal impedance with pH; PPI, proton pump inhibitor.

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