

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Overview of Refractory Gastroesophageal Reflux Disease



Rishi D. Naik, MD, MSCI
Assistant Professor of Medicine
Division of Gastroenterology, Hepatology and Nutrition
Vanderbilt University Medical Center
Nashville, Tennessee

G&H How prevalent is refractory gastroesophageal reflux disease?

RN In published reports, the prevalence of refractory gastroesophageal reflux disease (GERD) despite proton pump inhibitor (PPI) therapy has ranged from 10% to 54%. There is a reason that the prevalence of refractory GERD varies widely. Prevalence data are based on 3 categories of patients that different clinicians have defined as having GERD. One category includes patients who report symptoms of heartburn and regurgitation but have no confirmed diagnosis. Another category consists of patients in whom GERD has been diagnosed and whose symptoms may be GERD or an overlapping condition. The third category includes patients who have undergone functional testing to objectively confirm a GERD diagnosis. Thus, the prevalence of refractory GERD varies widely because symptoms of suspected patients have not always been objectively proven to be GERD. A key point regarding management is to first determine which category a patient represents.

G&H What best defines refractory GERD clinically then?

RN The recent consensus by the European Society of Neurogastroenterology and Motility and the American Neurogastroenterology and Motility Society did a great job of defining refractory GERD. The take-home message was that clinicians need to reconsider whether persistent symptoms of heartburn and regurgitation despite treatment constitute refractory GERD as per the Montreal

classification. Although the consensus definition fulfills the aforementioned first category of patients with refractory GERD, there has not been diagnostic confirmation of GERD. Thus, a patient's symptoms may or may not be related to true heartburn.

In the second category, a clinician has confirmed the presence of GERD and distinguished it via endoscopy from, for example, Barrett esophagus or a peptic stricture. If reflux testing was performed and the patient's GERD was confirmed and managed, the clinician should assess whether the patient's current symptoms are caused by GERD or a different condition.

In the third category, GERD has been confirmed and managed, and the reason for breakthrough symptoms has also been confirmed via further testing.

G&H What risk factors or predisposing factors should clinicians be aware of regarding refractory GERD?

RN Patients with a higher body mass index are at greater risk for GERD, and obesity strongly correlates with GERD risk. The presence of a large hiatal hernia or any dysfunction in the esophagogastric junction (EGJ) also increases risk for refractory symptoms. Patients who have dyspepsia, bloating, and/or fullness have a higher risk of refractory symptoms of reflux. Female sex and the presence of an autoimmune condition are also associated with a higher risk for refractory GERD. Anxiety or hypervigilance is a factor as well. The most common symptoms leading to refractory symptoms of reflux are nighttime symptoms, including sleep disturbances.

Medication nonadherence or incorrect use of medication also plays a role in refractory GERD. Sometimes the issue lies in deficits in physician-patient communication. For example, a clinician may not tell a patient how to take a PPI. It is not uncommon for a patient on an acid-suppressant medication such as a PPI to take a dose before going to bed or first thing in the morning, when the patient should be taking it 30 minutes to an hour before a meal. Such a patient tends to return to the doctor's office complaining of symptoms. Appropriate patient education is the easiest intervention in the toolbox.

G&H What factors should be reviewed when exploring different causes of suspected refractory GERD?

RN When reviewing factors for refractory symptoms, the first question concerns whether there is a mechanical defect or disruption of the EGJ. When there is a disruption in that barrier, reflux will still occur through that open valve despite acid-suppressive therapy. Antireflux medicines and education about lifestyle modifications may or may not help. The persisting symptoms can be classified as refractory GERD.

The second factor and question to assess concerns suboptimal acid suppression. If a PPI is underdosed or not given at the right time, or if the patient is not taking it at the right time, acid suppression is thwarted. Perhaps the easiest action a clinician can take when a patient complains of refractory GERD is to ask when he or she takes the medication.

It is important to ask what the patient's symptoms are and whether they are responsive to the medication. If the main symptom is worsening belching or bloating, a condition other than true GERD may be present and needs to be assessed. The same applies to patients with symptoms of hypervigilance, anxiety, or depression. Supragastric belching and rumination syndrome are among the many conditions and diseases that can express themselves in ways that may mistakenly be labeled as GERD.

Genes play a role in refractory GERD as well. Genetic variations exist that predispose patients to the inability to metabolize certain PPIs. Such patients may have a better response to other types of medications.

G&H When should a patient be referred for mental health evaluation?

RN The role of the gut-brain axis continues to expand, and the utility of neuromodulation has a real role for refractory symptoms.

Typically, most gastroenterologists, and most clinicians in general, do not refer patients for a full psychiatric evaluation and do not have clinics set up to do so. Rather, providers will—or should—walk the patient through management of comorbid depression and anxiety. Many medications used to manage refractory symptoms of GERD treat concomitant depression or hypervigilance. If comorbid depression or anxiety is an issue, a tricyclic antidepressant can be prescribed because of its neuromodulatory effects on the gastrointestinal tract.

G&H How does neuromodulation play into the assessment and management of refractory GERD?

RN Neuromodulation and the microbiota are 2 major frontiers in the field now. The efficacy of neuromodulation in the context of GERD may be difficult to grasp because neuromodulatory effects cannot necessarily be detected via endoscopy or even manometry. Neuromodulatory issues likely exist in GERD, but testing for them, as of yet, does not. Clinicians may want to consider that neuromodulatory effects may underlie some cases of refractory symptoms of GERD.

G&H What are the preferred diagnostic procedures for distinguishing refractory GERD from other conditions?

RN Obtaining objective evidence of GERD is needed. If a patient presents complaining of GERD symptoms but has not received a formal diagnosis, endoscopy and reflux testing while off medication are most helpful. GERD also needs to be distinguished from differential diagnoses and comorbid conditions. Thus, the EGJ should be assessed, as should the presence of a hiatal hernia. A barium esophagram can be helpful as a noninvasive tool for visualizing defects; however, an endoscopy not only assesses the EGJ but can identify inflammation, achalasia, and eosinophilic esophagitis. Biopsies may be needed. The clinician should also look for autoimmune skin conditions.

For refractory symptoms of GERD, manometry should also be part of the diagnostic algorithm, which can help identify rumination syndrome. Furthermore, multichannel intraluminal impedance-pH (MII-pH) testing while on therapy is an important tool for patients who have proven GERD with persistent symptoms. Indeed, MII-pH testing while on therapy has taken over as a key tool when endoscopy fails to uncover the cause of symptoms. Novel measurements and metrics can be achieved with impedance testing, such as postreflux swallow-induced peristaltic wave and mean nocturnal baseline impedance (MNBI).

G&H How is treatment for refractory GERD best approached?

RN Lifestyle modification is a major treatment pathway. Obesity, which is a major risk factor for GERD, is associated with intragastric pressure, which will cause heartburn and reflux. Obese and overweight patients should be referred for medical weight loss management. Surgery is another option in the case of morbid obesity or a large hiatal hernia.

PPI use for acid suppression should be optimized. Because nighttime heartburn is problematic for patients, an adjunctive H₂ receptor antagonist can be prescribed for nighttime use. Alginate can be used as a barrier effect between the stomach and esophagus.

G&H What treatment advances should clinicians be aware of?

RN Tools such as MNBI and assessment of total reflux events are ways of using different metrics and algorithms to help increase the yield of true refractory GERD. Improved diagnostic cutoffs using MII-pH testing have helped better define abnormal reflux parameters while patients are on therapy. The difficulty with MII-pH testing is that it is performed transnasally over a 24-hour period and may not be available at all centers. In comparison, a novel device that tests mucosal integrity (MI) (commercially available as MiVu, Diversatek Healthcare) has recently been approved by the US Food and Drug Administration for diagnostic testing of GERD. This device is used during endoscopy and tests MI

instantaneously to help identify abnormal mucosal changes, which can help identify GERD during endoscopy. Research is showing that MI testing can distinguish between eosinophilic esophagitis and GERD. Studies are ongoing on the ability of MI testing to define mucosal changes in patients with nonerosive esophagitis.

The goal is real-time diagnostics with applicability in long-term clinical care for a very complex disease. Long-term studies are currently in progress that will not only clarify diagnostic issues but may shed light on the long-term predictive value of antireflux surgery and medication management as well.

Disclosures

Vanderbilt University Medical Center co-owns the patent of MiVu. Dr Naik has no relevant conflicts of interest to disclose.

Suggested Reading

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