

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Approach to Management of Refractory Gastroesophageal Reflux Disease



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G&H What are important considerations in the evaluation of refractory gastroesophageal reflux disease?

RY Most important is to use the term *refractory gastroesophageal reflux disease* (GERD) correctly. Recent guidelines from the American College of Gastroenterology and recommendations from the European Society of Neurogastroenterology and Motility/American Neurogastroenterology and Motility Society define refractory GERD as a patient who has objective evidence of GERD (results of testing with either endoscopy or reflux monitoring show proof of GERD) and has undergone a trial of treatment, including optimized acid suppression and lifestyle management, but who continues to experience reflux-like symptoms. This is an important distinction from the patient with symptoms of GERD (eg, heartburn or regurgitation) who is not responding to acid suppression. In this latter scenario, the patient has not been formally diagnosed with GERD to begin with. Many mechanisms can cause GERD symptoms, and they are not always from true GERD itself.

G&H What diagnostic tests should be performed to confirm refractory GERD?

RY Again, a patient who has refractory GERD by definition has already had initial testing that confirmed GERD at baseline. This may include one of two tests: upper endoscopy that showed Los Angeles B, C, or D erosive esophagitis or long-segment Barrett esophagus; or ambulatory reflux monitoring performed off of acid

suppression that showed elevated acid exposure and/or elevated reflux events. If the patient fits one of these criteria and has persistent symptoms despite optimized therapy, the question is whether additional diagnostic tests are needed. Additional reflux testing is not always required. For instance, in a patient with a large hiatal hernia with regurgitation and already proven GERD, a practitioner

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may have a high level of confidence that the patient has true refractory GERD and can proceed with further escalation of therapy or consideration of more invasive interventions. However, when there is uncertainty as to whether the patient truly has ongoing reflux disease or an overlap from another entity (eg, a behavioral condition), then additional testing can be valuable. In this case, the

test of choice is impedance pH monitoring performed on double-dose proton pump inhibitor (PPI) therapy. An elevated acid exposure time and/or elevated number of reflux events are diagnostic of refractory GERD. Other data on impedance pH monitoring such as symptom reflux association or mean nocturnal baseline impedance can provide valuable adjunctive evidence to support or refute a diagnosis of refractory GERD.

Impedance pH monitoring is preceded by a manometry study to localize the lower esophageal sphincter (LES) and guide placement of the impedance pH catheter. High-resolution impedance manometry has several diagnostic roles in this patient population. Most importantly, it is used to rule out achalasia, which can masquerade as GERD. This is pivotal to avoid delay of achalasia treatment. In addition, manometry can identify other mimickers of GERD (eg, rumination syndrome or a supragastric belching disorder). It is critical to identify these manometry patterns because the treatment may be very different from that of GERD. For instance, management of rumination syndrome often involves nonsurgical behavioral therapy. Again, the results of these tests can prevent mismanaging or misdirecting the management of patients.

G&H How is PPI therapy optimized for refractory GERD?

RY The first step is to ensure that the PPI is being taken appropriately. This requires that PPI therapy is taken before meals and on a regular schedule. Merely adjusting the time of PPI dosing from bedtime to before dinner can make a tremendous difference. The next step is the potential to increase the level of gastric acid suppression. One way to do this is to increase from a single dose to double dose (eg, increasing omeprazole 20 mg, which is considered a single dose, to twice a day or to 40 mg once a day, which is the double dose). Also, it is important to remember that not all PPIs are the same. Although they share the same mechanism, some are metabolized more through the cytochrome P450 2C19 (CYP2C19) pathway than others. There is also a difference in potency. For example, pantoprazole is a less potent gastric acid suppressive therapy, whereas rabeprazole, esomeprazole, and dexlansoprazole provide more potent gastric acid suppression. Thus, one approach to PPI optimization is to consider switching to a more potent agent that is less metabolized through the CYP2C19 pathway (such as rabeprazole).

G&H What are the mechanisms of PPI-refractory GERD?

RY There are myriad mechanisms of PPI-refractory GERD. One mechanism is ongoing mechanical reflux

that can be seen when the antireflux barrier is disrupted (eg, a patient with a hiatal hernia with a hypotensive LES), or when there is increased intragastric pressure from, for instance, central obesity. Another mechanism is breakthrough acid exposure despite the patient being on an optimized PPI. When gastroesophageal reflux occurs, esophageal dysfunction can perpetuate refractory GERD. For instance, in a healthy state the esophagus will squeeze and propel the refluxate back into the stomach. However, in some patients, the motility in the esophagus is compromised and weak. In this scenario, there may be insufficient squeeze to clear the refluxate out of the esophagus. This is particularly pronounced at nighttime in supine positions, without the aid of gravity to keep refluxate down. In some cases, the esophageal epithelial mucosal integrity is reduced whereby nerve endings in the esophagus have heightened sensitivity to refluxate. Lastly, and probably most important, is the impact of cognitive affective processes (eg, hypervigilance, anxiety, and psychological influences). Patients who have had GERD and experienced troublesome symptoms even when their GERD is adequately controlled may have a heightened fear and a perseveration about these symptoms. If that cycle is not broken, then symptoms can persist.

G&H How can a personalized approach improve management of refractory GERD?

RY Historically, the approach has relied on acid suppression, which if unsuccessful, in some cases, has been followed by a surgical intervention. However, as discussed, many other mechanisms beyond acid or mechanical dysfunction can cause ongoing symptoms. It is pivotal for practitioners to pinpoint the actual mechanism, and thereby direct therapy. For instance, for reflux sensitivity-related mechanisms, neuromodulation with either low-dose antidepressants or with behavioral interventions can be helpful. Similarly for hypervigilance and anxiety, psychotherapy, hypnotherapy, or cognitive behavioral therapy methods can be very effective.

Lifestyle optimization is also paramount. A majority of my patients find substantial improvement with lifestyle modifications, and even if not 100% improvement, they achieve a quality of life where escalation of therapy is not needed. Some are even able to discontinue their PPIs. Lifestyle modification refers to methods to reduce the volume and the pressure in the stomach. These include weight loss, particularly reducing abdominal or visceral fat, and not wearing tight-fitting clothing around the abdomen. Patients can also try to reduce the size of meals, particularly at dinnertime, and wait 3 hours between dinner and recumbency, not just in bed but even while watching TV or reading a book. If a patient is waking up

in the middle of the night with symptoms, then elevating the head of the bed using structured support (eg, bricks under the head of the bed, a wedge pillow, or a medical bed) and laying on the left side can be helpful.

G&H What pharmacologic options are considered for managing PPI nonresponders?

RY This comes back to the mechanism of refractory GERD. For suspected breakthrough acid, adding a histamine receptor antagonist, particularly at nighttime, has been shown to reduce nocturnal acid and nocturnal

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symptoms. In addition, potassium-competitive acid blockers (P-CABs), which are available in some countries, are effective for erosive esophagitis and may have a role in the treatment of refractory GERD as well.

For patients with mechanical causes of refractory GERD, one consideration is alginate antacids, particularly for postprandial symptoms and in patients with hiatal hernia. Alginate antacids have been shown to effectively reduce reflux symptoms in randomized, placebo-controlled trials. Another option is transient LES relaxation (TLESR) inhibition with γ -aminobutyric acid type B receptor agonists, such as baclofen. Based on studies and anecdotal experience, TLESR inhibitors are likely most helpful in patients with belch-predominant reflux. Use of TLESR inhibitors can be limited owing to drowsiness and gastrointestinal side effects that can be difficult to manage.

Again, if hypersensitivity or anxiety is suspected, neuromodulation with antidepressants can be helpful in PPI nonresponders. Although research does not support use of prokinetic therapies (such as metoclopramide) for GERD, there may be a role for these therapies in patients with GERD and overlapping gastroparesis.

G&H Which patients with refractory GERD may benefit from endoscopic therapy?

RY Endoscopic therapy such as transoral incisionless fundoplication is an option for patients with objective GERD who require acid suppression for symptom control but do not want to remain on long-term acid suppression. Generally, endoscopic therapy is coupled with a laparoscopic crural repair and hiatal hernia repair in patients with a defective antireflux barrier.

G&H What are the pros and cons of surgical approaches for refractory GERD?

RY Surgical approaches include fundoplication, a full 360° wrap or partial wrap; magnetic sphincter augmentation; and Roux-en-Y gastric bypass, which is a bariatric surgical procedure but also effective as an antireflux procedure. Generally, fundoplication and magnetic sphincter augmentation are technically effective antireflux surgical approaches to restore the antireflux barrier and recreate the flap valve. As a result, they have high rates of success in reducing GERD and are a treatment option to consider for patients with PPI-refractory GERD.

Studies show that somewhere between 30% and 50% of patients will be on PPI therapy in the long term even after surgery. PPI resumption after surgery is not considered a failure of the surgery. It is possible that patients resume medications because of persistent symptoms unrelated to gastroesophageal reflux events (eg, hypervigilance). Furthermore, over time the integrity of the surgery may decline, and adjunctive PPI therapy can help provide breakthrough relief. It is always important to remember that surgical approaches are invasive and are not without risks, both during the time of surgery and in the long term. Side effects can be difficult for patients and may have a significant impact on quality of life. These include the potential for gas-bloat syndrome, dysphagia, inability to belch, and inability to vomit. Also, it is important to address psychological overlapping conditions prior to surgery and manage patient expectations about symptom relief following surgery as well as the potential for long-term effects and PPI resumption.

G&H When is pharmacologic neuromodulation or referral to a behavioral therapist recommended?

RY It is valuable to introduce the concept of gut-brain interaction with all patients and to consider these treatment options, particularly for patients exhibiting elevated levels of anxiety, hypervigilance, or increased symptoms around times of stress. Referral to a behavioral therapist is

a good option for a patient who does not want to be on a medication, but particularly for a patient who is open and accepting of a behavioral therapeutic approach because not all patients are.

G&H What new developments in treatment are most important for clinicians?

RY At present, the major paradigm shifts in GERD surround the movement toward personalized management and the overlap of GERD with cognitive affective processes, as well as empowering and educating patients about these processes. In terms of novel pharmacologic therapy, P-CABs are currently approved by the US Food and Drug Administration for *Helicobacter pylori* eradication and are being reviewed for erosive esophagitis based on the results of positive phase 3 trial data for erosive esophagitis and new data emerging for GERD. Other areas of interest are whether data from manometry should guide treatment decisions for patients considering an endoscopic or surgical antireflux procedure, and whether patients with weak motility are at increased risk for postoperative dysphagia following a complete fundoplication, the latter of which is an area of controversy.

Disclosures

Dr Yadlapati is a consultant for Medtronic (institutional), Phathom Pharmaceuticals, and Med DataLink (institutional). In addition, she receives research support for Ironwood Pharmaceuticals and is on the advisory board, with stock options, of RJS Mediagnostix.

Suggested Reading

Halland M, Bharucha AE, Crowell MD, Ravi K, Katzka DA. Effects of diaphragmatic breathing on the pathophysiology and treatment of upright gastroesophageal reflux: a randomized controlled trial. *Am J Gastroenterol.* 2021;116(1):86-94.

Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. *Am J Gastroenterol.* 2022;117(1):27-56.

Patel A, Yadlapati R. Diagnosis and management of refractory gastroesophageal reflux disease. *Gastroenterol Hepatol (NY).* 2021;17(7):305-315.

Yadlapati R, DeLay K. Proton pump inhibitor–refractory gastroesophageal reflux disease. *Med Clin North Am.* 2019;103(1):15-27.

Yadlapati R, Gyawali CP, Pandolfino JE; CGIT GERD Consensus Conference Participants. AGA Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD: Expert Review. *Clin Gastroenterol Hepatol.* 2022;20(5):984-994.e1.

Yadlapati R, Vaezi MF, Vela MF, et al. Management options for patients with GERD and persistent symptoms on proton pump inhibitors: recommendations from an expert panel. *Am J Gastroenterol.* 2018;113(7):980-986.