ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Proton Pump Inhibitor Nonresponders

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G&H What is the best definition of a proton pump inhibitor nonresponder?

BL In my opinion, the best definition of a proton pump inhibitor (PPI) nonresponder is a patient with symptoms of gastroesophageal reflux disease (GERD) who has failed double-dose PPI therapy for at least 8 to 10 weeks. However, there have been questions about this definition—for example, is a PPI nonresponder someone who has not responded based solely on symptoms (recognizing that clinicians and patients ask about and report symptoms differently), based on endoscopic findings, or based on pH testing? On the other hand, should the term be defined based on the dose (ie, 20 mg or 40 mg) or frequency (ie, daily vs twice daily) of the medication? It is still not clear exactly how a PPI nonresponder should be defined. One of our goals should be to clarify whether a PPI nonresponder applies just to the GERD population—because that is where PPIs are used most often—or to other populations as well.

G&H Why is this issue clinically relevant?

BL PPI nonresponse is a clinically important issue for a number of reasons. PPIs are overprescribed. In 2009, there were 110 million prescriptions for PPIs. Three of the top 13 prescribed medications are PPIs, and approximately 13 billion dollars are spent each year on PPIs just in the United States. Therefore, this issue has important economic implications to our health care system.

Perhaps more importantly, there are emerging data that PPIs may have some medical risks. For example, there is a slight increased risk of community-acquired pneumonia while on a PPI as well as a slight increased risk of an enteric gastrointestinal infection. There may be an association between PPI use and the risk of fracture, although this is controversial. Many of the studies that support this association have been retrospective or observational in nature; large randomized placebo-controlled studies to guide clinical practice are not available. That being said, there is a slight increased risk for fracture, with an odds ratio of 1.56 for spine fracture and an odds ratio of 1.3 for hip fracture. However, it is unclear whether this risk is associated with only a particular type of PPI, whether a double dose is worse than a single dose, whether the length of therapy plays a role, and of course whether specific patients are at increased risk due to genetic factors, comorbid conditions, or use of other medications. Although these risks are quite low, clinicians should always carefully review why patients are taking PPIs and discontinue therapy if it is not clinically warranted.

G&H Being that PPIs are often quite effective in patients with GERD, why do some patients fail to have a response?

BL Patients do not respond to PPIs for a number of reasons. The first reason is that patients may have a disorder that does not respond to PPI therapy (ie, a condition other than reflux esophagitis or GERD). Some clinicians use PPIs to treat other conditions, such as irritable bowel syndrome, nausea, or functional dyspepsia, even though PPIs have never been shown to improve these conditions or, in the case of functional dyspepsia, have been shown to help only a small group of these patients.

The second reason that patients might not respond well to PPI therapy is that their predominant symptom is regurgitation. PPIs have been shown to be excellent medications for reflux esophagitis. When comparing the cardinal symptoms of reflux (pyrosis or substernal burning vs regurgitation), PPIs are more effective at treating pyrosis or substernal burning than regurgitation. Therefore, some patients may present with reflux symptoms, be treated with a PPI, improve in terms of their symptoms of pyrosis and the healing of their esophagitis, but they may still have symptoms of regurgitation because that symptom does not respond as well to a PPI.

G&H How should these patients be evaluated?

BL When a patient presents with GERD symptoms that have not improved with PPI therapy, the first step is to obtain a thorough patient history. One of the most common reasons that patients with GERD do not respond to PPI therapy is that they are not compliant with the medication. Several studies have shown that at the end of 1 month, only approximately 50% of patients are taking their PPIs appropriately. Many patients have never been appropriately counseled on how to take a PPI, and approximately 52% of patients take their PPIs at bedtime, which has been shown to be much less effective. The best time to take a PPI is in the morning on an empty stomach, and then the patient should wait approximately 30 to 45 minutes before eating breakfast. Therefore, the first thing that I check is patient compliance, and then I make sure that the patient is taking his or her PPI correctly in terms of timing.

Another reason that patients may not respond to PPI therapy is that they might be on too low of a dose; whether it is 20 mg of omeprazole or esomeprazole, some patients may need a higher dose once daily (ie, 40 mg of omeprazole or esomeprazole).

In addition, nonresponse may come back to whether a patient has other disorders that may not respond to PPI therapy, as discussed above, or whether the patient has other diagnoses that coexist with GERD, such as esophageal motility disorders, eosinophilic esophagitis, gastroparesis, or rumination syndrome. In suspected cases of comorbid disorders, it might be helpful to have the patient undergo esophageal manometry to look for an esophageal motility disorder (such as achalasia or diffuse esophageal spasm) or undergo pH testing (which might include impedance pH testing using a transnasal probe) while on a daily PPI to see if the patient is still experiencing acid breakthrough or nonacid reflux. Another test that could be considered is a 4-hr gastric emptying study to determine whether a patient has a significant delay in gastric emptying that might lead to symptoms, which the patient may mistake for PPI nonresponse. If a patient had significant esophagitis in the past, and the clinician needs to document healing or the clinician is worried that the patient's symptoms might represent eosinophilic esophagitis and biopsies were not obtained in the past, a follow-up upper endoscopy might be reasonable, with biopsies in the distal and middle of the esophagus to look for eosinophilic esophagitis or lymphocytic esophagitis.

G&H Can pH testing predict response to PPI therapy?

BL Unfortunately, no. It would be helpful if clinicians could perform appropriate pH testing (a 48-hr wireless pH capsule test or a transnasal impedance pH probe) and then use parameters on the pH test that would help predict response to therapy. Unfortunately, this is not yet possible.

G&H When is pH testing indicated, and how useful is it in this setting?

BL At least in my practice, pH testing is indicated in a number of different situations. The first would be when I think a patient clearly has true GERD, I place the patient on a PPI, and the patient is still experiencing persistent symptoms despite taking the medication appropriately. I would evaluate such a patient with either a transnasal impedance pH probe or a 48-hr wireless pH capsule. Several studies have now shown that the vast majority of patients with reflux symptoms do not require a double-dose (or even higher dose) PPI, and I tend to test patients earlier rather than later to show that their acid is controlled on a daily PPI, before treating the patient for months with double-dose therapy that may not be required or be effective.

I also perform pH testing when a patient presents with extraesophageal manifestations, such as constant clearing of the throat, vocal cord problems, chronic cough, or asthma symptoms, and the patient reports that these symptoms are not responding to PPI therapy. (This is a frequent referral to our Motility Center in which another provider may have thought that these symptoms represented reflux and put the patient on a PPI.) In this situation, I would take the patient off the PPI and examine him or her with a 48-hr wireless pH capsule.

G&H Is it cost-effective to perform pH testing early rather than later in PPI nonresponders?

BL Especially nowadays when medical costs are rising and budgets are limited, I think that all clinicians need to try to practice medicine as cost-effectively as possible. Therefore, the following question has often come up: is it more cost-effective to place patients on PPI therapy, often

escalating from a daily dose to a twice-daily dose, or is it more cost-effective to measure patients upfront to determine whether acid reflux is the culprit, and then place the patients on the appropriate therapy? This question has come up in part because the symptoms of acid reflux are not very sensitive or specific. Even a well-established, astute clinician can sometimes find it very difficult to determine whether the upper abdominal symptoms described by a patient truly are acid reflux, as opposed to the other conditions previously mentioned, such as functional dyspepsia, ineffective esophageal motility, or eosinophilic esophagitis.

With all of this in mind, my colleagues and I conducted a cost economic analysis several years ago. Using economic modeling, we found that upfront pH testing, using a 48-hr wireless pH capsule test, was more cost-effective than placing patients on long-term PPI therapy. pH testing, which cost the insurance company very little, was able to identify patients who did not have acid reflux and enabled them to avoid unwarranted PPI therapy.

This concept of upfront testing is important. Although pH testing is associated with more costs than simply doubling the dose of a PPI for a few weeks, what typically happens is that patients are placed on a double-dose PPI, and they continue that dose for months or even years without any clinical need. This long-term therapy thus becomes quite expensive and, as mentioned earlier, increases the risk of fracture. More importantly, it delays making the correct diagnosis (eg, eosinophilic esophagitis, functional dyspepsia), which then delays initiating appropriate therapy.

G&H How should these patients be treated?

BL The first step is to identify whether a patient truly has acid reflux and needs to be on a PPI (or at a higher or more frequent dose) or whether the patient does not have acid reflux at all, going back to the testing mentioned before. In other words, if the pretest probability of acid reflux is low, the patient should be measured off PPI therapy using a 48-hr wireless pH capsule. If the probability is moderate or high, then pH testing can be performed using impedance pH monitoring.

With this paradigm in place, other options can be considered to improve reflux symptoms in PPI nonresponders. For example, some patients may find some benefit with baclofen, which reduces the frequency of transient lower esophageal sphincter relaxations. Other patients may do better on a coating agent, such as sucralfate. Some clinicians believe that bile acid sequestrants can be very useful because they bind bile; however, there are no prospective studies in the literature to date to support this practice. Many PPI nonresponders have some degree of visceral hypersensitivity in their esophagus, especially those with overlapping functional dyspepsia or irritable bowel syndrome; thus, a low-dose tricyclic antidepressant taken in the evening may be very helpful. Dr Ronnie Fass and colleagues conducted an interesting study showing that acupuncture is better than escalating a patient from a once-daily PPI to a twice-daily PPI. However, that study has not yet been replicated.

Finally, many patients and providers become very frustrated when patients experience persistent symptoms and do not respond to therapy. Some of these patients and providers turn to surgery, looking for rapid symptom relief. However, we should be very cautious about approaching surgery as an option in this setting because the patients who respond best to surgery are those with classic symptoms of reflux and esophagitis who respond to a PPI. Patients with normal endoscopic findings and normal study results who are having persistent symptoms on a PPI are much less likely to respond to surgery.

Dr Lacy has served on scientific advisory boards for Given/Covidien, Takeda, Prometheus, and Ironwood. He has received grant support from the National Institutes of Health (functional dyspepsia treatment trial) and has received investigator-initiated support for an irritable bowel syndrome trial from Takeda.

Suggested Reading

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