ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Helicobacter pylori Infection in the Era of Antibiotic Resistance

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G&H How significant of a problem is antibiotic overuse?

NS Although gastroenterologists might think that antibiotic overuse does not affect them, they actually use antibiotics quite often. Prescription rates for clarithromycin, the most commonly prescribed antibiotic for *Helicobacter pylori* treatment, have skyrocketed in recent decades, as have the rates for quinolones. Although many of these prescriptions are appropriate and needed, many are not. The National Committee for Quality Assurance maintains a list of "antibiotics of concern" that are overused, and clarithromycin was recently added to this list. Although the data on this issue are still limited and imperfect, recent investigations of patients with *H pylori* infection have reported an increase in clarithromycin resistance from 13% in 2004 to 18% in 2015 as well as a concomitant drop in pan-susceptible strains from 66% to 51%.

One of the consequences of antibiotic overuse is the development of resistant strains of bacteria, including *H pylori*, as well as an increased prevalence of *Clostridium difficile* infection. An abstract at the 2015 American College of Gastroenterology (ACG) meeting reported that the use of antibiotics for *H pylori* treatment is indeed associated with an increased risk of *C difficile* infection.

In fact, in 2014 the White House and the Centers for Disease Control and Prevention declared antibiotic overuse and the lack of antibiotic stewardship akin to a state of emergency. They then issued a national strategy, which is budgeted for fiscal year 2016, for combating antibiotic-resistant bacteria that addressed several components, including the tracking of antibiotics, development of new compounds, and improvement of antibiotic stewardship. The last component involved a commitment to use antibiotics only when needed, to choose the appropriate antibiotics, and to administer antibiotics safely. However, it turns out that not all clinicians are doing very well at meeting these goals when it comes to *H pylori* treatment.

G&H How prevalent is *H pylori* infection in the United States?

NS Overall, approximately 30% of the adult population and 25% of the pediatric population have evidence of *H pylori* infection. These figures reflect the entire population, but can vary widely, from 80% in an elderly, lower socioeconomic, immigrant community to approximately 10% in a young, upper socioeconomic, predominately US-born population. We do know that the infection is transmitted person-to-person and is usually acquired in childhood.

G&H What are the clinical consequences of *H pylori* infection?

NS Essentially all patients with *H pylori* infection develop histologic gastritis. Clinical consequences of *H pylori* infection can range from dyspepsia and peptic ulcers to gastric cancer. *H pylori* has been classified by the World Health Organization as a Group 1 carcinogen, meaning that it has a definite association with the risk of cancer. In addition to gastric adenocarcinoma, *H pylori* infection also increases the risk of developing gastric

mucosal-associated lymphoid tissue (MALT) lymphoma. If detected early, MALT lymphoma is often treatable by eradicating *H pylori* infection.

G&H When is *H pylori* testing appropriate?

NS According to the 2007 ACG guidelines, testing for *H pylori* infection should be undertaken in patients with current or past peptic ulcer disease, those with gastric MALT lymphoma, or those with early gastric cancer. It should be noted that these guidelines are somewhat outdated and are currently being revised.

Other indications for testing have been suggested; some of these are likely appropriate, while others are less so. One proposed indication is nonulcer dyspepsia, and I agree that this should, in fact, be an indication for testing, particularly in a high-risk population, such as elderly or non–US-born individuals. On the other hand, some doctors have suggested that gastroesophageal reflux disease (GERD) might be a potential indication for *H pylori* testing. Current data, however, do not support an association between the 2 conditions; in fact, the conditions may be inversely related, with *H pylori* potentially protecting against GERD. This relationship still has not been definitively established, but I would advise against the routine testing of *H pylori* infection in patients with GERD.

Long-term nonsteroidal anti-inflammatory drug (NSAID) use has also been suggested as an indication for *H pylori* testing, according to the Maastricht guidelines. I would not suggest retroactively testing all patients who have already been established on NSAID therapy, but if a patient comes in with a new diagnosis requiring long-term NSAID therapy, *H pylori* testing should be performed prior to the initiation of therapy to lower the risk of NSAID-related complications.

Iron deficiency has also been associated with *H pylori* infection, although it is debatable whether this relationship is causal.

Finally, it has been suggested that patients at an increased risk for gastric cancer should be tested. I think that this is very reasonable, particularly for those with a family history of gastric cancer. If a patient's mother had stomach cancer, it is highly likely that the cancer was related to *H pylori* infection. Mother-to-child transmission is known to be one of the best predictors of having *H pylori* infection, so it is reasonable to check the children of an infected woman, as this might be the one remediable factor that can be addressed.

G&H How well are the *H pylori* testing guidelines being implemented?

NS Based on claims data, it turns out that the guidelines are not being followed very well. An analysis of claims of nearly 8000 patients who received treatment for *H pylori* infection found that approximately one-third of patients had never been tested for the condition and were being treated empirically, a practice that is not supported by any clinical guideline that I am aware of. Excellent testing for *H pylori* infection is available; clinicians should be testing patients and treating patients who test positive.

In a more recent database analysis of over 230,000 patients with claims for *H pylori* treatment, confirmatory pretreatment testing was only identified in 41% of patients. As claims data, both of these studies have flaws, and some testing may have been performed outside of the database. However, these findings do suggest very imperfect adherence to guidelines.

G&H What types of diagnostic tests are available for *H pylori* infection?

NS The *H pylori* diagnostic tests currently available can be generally characterized as endoscopic or nonendoscopic. Endoscopic tests are appropriate if the patient has any type of indication for endoscopy; endoscopy is generally not performed solely for the purpose of looking for *H pylori* infection. Endoscopic testing options include a rapid urease test and histology. Cultures are not widely used in the United States.

Three nonendoscopic options are currently available. The first is serologic testing, which detects the presence of *H pylori*–specific antibodies in the blood. This type of testing is not recommended, as it is actually a test of *H pylori* exposure rather than a test of active infection. Patients can remain *H pylori* antibody–positive for months or even years after the infection has been eradicated. Moreover, serology testing has a poor positive predictive value in low-prevalence populations. Based on these drawbacks, serology testing is not generally recommended by clinical guidelines. However, claims data indicate that serology testing is still widely used. This may change soon, as some health care plans are no longer covering serology testing for *H pylori* infection, and some laboratories are no longer offering it. Gastroenterologists should educate their community primary care physicians about using less serology.

The other 2 diagnostic tools test for active infection. One is a urea breath test (UBT), which previously used the ^{14}C radioactive isotope and now uses the ^{13}C nonradioactive isotype. A commercially available UBT (BreathTek, Otsuka) is a reasonable test for both initial diagnosis and eradication testing of *H pylori* infection in adults and in children at least 3 years old. The test detects active infection and has excellent positive and negative predictive values. It has demonstrated excellent accuracy in adults, with sensitivity and specificity rates of 95% and 90%, respectively, for initial diagnosis and 96% for both sensitivity and specificity in the posttreatment period.

The other option is a stool antigen test. This test is also very accurate, but it requires stool collection and transporting the sample on ice. Surveys have shown that more patients prefer the breath test to the stool test and are more likely to return for posttreatment testing if the breath test is offered. However, despite the more cumbersome nature of the stool test, its accuracy is comparable to that of the breath test.

G&H How is urea breath testing performed?

NS The UBT is accessible in a variety of settings. Direct in-office units are available that can provide results within 15 minutes, which is how I use the test; this allows for immediate feedback to the patient, who is already in the office, and, if the test results are positive, treatment can be initiated immediately. For practices that do not have a high volume of testing, breath samples can be sent to a laboratory for analysis, or the patient can be sent to a laboratory for testing and breath sample analysis.

G&H What are the current approaches to treatment of *H pylori* infection?

NS There are 2 *H pylori* treatment regimens that are currently approved by the US Food and Drug Administration (FDA) and supported by guidelines, and these have not changed since 2007. The first is a clarithromycin-based triple therapy consisting of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole for 14 days. The other option is bismuth quadruple therapy, which consists of a PPI or an H_2-receptor antagonist plus bismuth, metronidazole, and tetracycline for 10 to 14 days. Eradication rates with these approaches are abysmal in my opinion—approximately 70% with triple therapy and 78% with bismuth quadruple therapy—and are probably declining, in large part due to clarithromycin resistance.

G&H What are the treatment options for persistent *H pylori* infection?

NS Several salvage treatment options are available. Retreatment with the therapy that was used initially would be fruitless and is advised against. However, the option that was not used for initial therapy can be used for salvage therapy (either quadruple therapy or triple therapy).

If that does not work, no other FDA-approved options are currently available, although several strategies have been investigated. There are reasonably strong European data for levofloxacin-based therapies; however, high rates of levofloxacin resistance are now being reported.

Sequential therapy has also been evaluated; this strategy attempts to bypass resistance by using 1 antibiotic followed by the other. Patients receive a PPI plus amoxicillin for 5 days followed by a PPI plus clarithromycin and tinidazole/metronidazole for 5 days. This approach works reasonably well.

A third approach is concomitant therapy, which basically combines triple and quadruple therapy. Patients receive a PPI, clarithromycin, metronidazole/tinidazole, and amoxicillin for 3 to 7 days. This approach has yielded reasonable results that are better than the results attained with triple or quadruple therapy. However, more effective salvage regimens are clearly needed, as well as more data on the US population.

G&H Does the eradication of *H pylori* infection reduce the risk of related complications?

NS Yes, there are strong data showing that eradication of *H pylori* infection reduces the risk of peptic ulcers, NSAID-related ulcers, dyspepsia, and likely gastric cancer, if treated early in its natural history. However, the relative risk reduction of each complication varies. For example, the number needed to treat (NNT) to reduce duodenal ulcer risk is only 2, while the NNT to reduce dyspepsia is higher (reportedly 9-12), as there are many causes of dyspepsia in addition to *H pylori*.

G&H When is posttreatment testing appropriate to confirm *H pylori* eradication?

NS The current but dated ACG guidelines recommend selective posttreatment testing, with testing advised in patients with ulcers, those with gastric cancer, and patients with persistent symptoms. However, the same guidelines that recommend selective testing based on symptoms also note that symptoms are a poor predictor of *H pylori* infection status.

More recent pediatric guidelines do recommend routine posttreatment testing in all pediatric patients and note that testing should be performed even in asymptomatic children, given that the absence of symptoms does not mean that the infection has been eradicated. Granted, these are children, who have many years in front of them, so perhaps they should be treated differently from adults. On the other hand, it could be argued that clinicians should also be performing routine posttreatment testing for adults as well, particularly given the declining eradication rates. With the current low treatment efficacy rates of approximately 65% to 70%, I believe that it is appropriate to check for eradication in all patients.

G&H How frequently is posttreatment testing performed in the United States?

NS The same claims databases that showed suboptimal initial testing rates found that only 13% to 15% of

patients receive posttreatment testing. That number probably does not need to be 100%, but it should be substantially higher than 13%.

This column is based on a 2015 American College of Gastroenterology presentation sponsored by Otsuka.

Dr Stollman is on the speakers bureau for Otsuka.

Suggested Reading

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