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How We Approach Difficult to Eradicate *Helicobacter pylori*

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Gastroenterologists spend much of their working lives focused on cancer prevention through an array of approaches, including screening and surveillance colonoscopy, endoscopic surveillance of Barrett's esophagus, investigating pancreatic cysts noted incidentally, and investigating symptoms that patients are concerned may be the harbingers of malignancy. *Helicobacter pylori* eradication should also be considered an important element of cancer prevention, because it has the potential of decreasing gastric cancer by about 50%.[1] Although less immediately gratifying than endoscopic interventions, *H pylori* eradication has its own challenges, requiring time, thought, and, most important, buy-in from patients who may not understand the reasons for, or the complexity of, the prescribed regimen.

Because *H pylori* infection is most prevalent in underserved, poor, and immigrant communities, it is particularly important to overcome the communication, trust, and economic barriers experienced in *H pylori* management, in addition to selecting appropriate antimicrobial agents. Time and patience are critical when discussing why the first treatment failed and identifying what should be done next. Unfortunately, all too frequently these tasks are left to an inexperienced fellow working in an academic medical center concentrated on the underserved, or a busy nurse practitioner who has been given the job of following up all such cases in a gastroenterology group practice.

Although we do not have any system in the United States to track the outcome of *H pylori* eradication therapy, it is likely that only about 70% of initial eradication attempts succeed. We review here our approach to those patients in whom treatments fail, with an emphasis on the practical considerations involved in achieving subsequent eradication success (Table 1). These practical aspects have been much less discussed in the literature than the many algorithms of drug combinations that are suggested for such refractory cases, usually based on antibiotic resistance awareness.[2] Although less evidence based, addressing the human and societal reasons behind why *H pylori* eradication treatments fail should help to avoid repeated unsuccessful antibiotic courses and help to achieve *H pylori* eradication in almost all cases.

Patient Education: *H pylori* Eradication Is Important, But Never an Urgent Matter

H pylori is usually acquired in infancy, yet typically not diagnosed until many decades later. Gastric cancer, the most feared outcome of *H pylori* infection, is mainly a disease of the elderly. Given the protracted timeline of many decades between the initial infection and the development of cancer, there is never a need to rush into prescribing treatment, especially after $\geq$1 unsuccessful attempts.

After failed attempts at *H pylori* eradication, a face-to-face office visit with the patient (or, given COVID restrictions, a video virtual visit) is recommended. This appointment is mandatory for those patients who are referred to us by other providers. At the appointment, a certified interpreter is essential for those many patients with *H pylori* infection who lack fluency in English. Important parts of the history include noting a family history of gastric cancer and a review of the endoscopic and pathological findings (if performed) to gauge how critical achieving eradication might be for that specific individual. Prior *H pylori* regimen(s), and any other past antibiotic use and adverse reactions, including real or perceived allergies, are important to document during this initial patient encounter.

At this visit, providers should attempt to understand the patient's fears and concerns regarding their diagnosis (including allaying the fear that cancer may be imminent, or guilt that the infection reflects their upbringing, or bad habits). It is also important to discuss *H pylori*'s acquisition in childhood and its dormancy and to reassure the patient that it is not a highly transmissible organism, especially among adults. Patients should be informed that successful *H pylori* eradication should decrease the rare chance of developing gastric cancer (from about 2 people in 100 to 1 in 100) or peptic ulcers (from about 10 to 3 people in 100), although their gastric symptoms may well persist; recall

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Table 1. Practical Tips for Difficult to Eradicate *Helicobacter pylori*

Providers should perform an initial in-person (or virtual) office visit to better understand the patient's symptoms and concerns.
A complete review of the medical history should be conducted for all patients with persistent *H pylori* infection, including prior treatment regimens, pathological findings (if available), and family history of gastric cancer
Given the complexity of treatment regimens, patients should be provided with detailed guidance such as correct dosing instruction, anticipated adverse effect, and rationale for retreatment,
Potential barriers to medication adherence should be explored before prescribing another treatment regimen, including high drug costs, medication misunderstandings, and communication barriers.
Given the importance of amoxicillin in refractory *H pylori* treatment regimens, penicillin allergy testing is encouraged to allow its delisting as an allergy (in most cases).
Tailored antibiotic selection through *H pylori* susceptibility testing should be considered when the choice of treatment is not obvious.
Gastric acid suppression is an important component to *H pylori* eradication. High and frequent doses of proton pump inhibitors not metabolized by *CYP2C19* are preferred, or potassium-competitive acid secretion inhibitors if available.
All patients treated for *H pylori* should have post-treatment follow-up by breath or stool test to confirm eradication.
In a small subset of patients, the benefit of multiple *H pylori* eradication attempts should be weighed against the risk of repeated antibiotic exposure.

that, for dyspepsia resolution, the number needed to treat is about 15.[3]

This 2-way exchange of information is an important prerequisite to successful *H pylori* eradication. In contrast with the much simpler concept of precancerous colon polyp removal to prevent colon cancer, discussing how eliminating a usually clinically silent bacterium can prevent stomach cancer and yet still fail to relieve a patient's current meal-related symptoms is a more complex conversation.

Understanding Why the Last Treatment Failed Will Improve Future Success

The usual reasons why *H pylori* eradication attempts fail is due to primary resistance to $\geq$1 of the antibiotics used, or failure to adhere to the complex multidrug eradication regimen (which can itself result in secondary or acquired resistance). The former is generally the responsibility of the prescriber, the latter is usually a shared failure, although the patient often takes the brunt of the blame.

Before embarking on a subsequent treatment, it is important to explore the details of prior eradication attempts. For example, what was prescribed may not be the same as what was taken home from the pharmacy (perhaps not all the medications were collected because of cost), the medication instructions may not have been followed as intended (the components should of course be taken concurrently as opposed to consecutively), or the patient may have stopped taking the medication before the end of the course because of side effects or because their symptoms did not improve (or may have worsened). The same regimen may have also been prescribed more than once (unfortunately this is far from rare). An incomplete understanding of what happened during the initial eradication attempt(s) may well doom subsequent treatments attempts.

The high pill burden, the required multiple dosing per day timed according to meals, the duration of treatment, and the side effects profile are some of the best-studied barriers to *H pylori* eradication regimen adherence. Although fixed-dose, all-in-one oral capsules (such as Pylera [a combination of bismuth, metronidazole, and tetracycline] and Talicia [rifabutin, amoxicillin, and omeprazole]) have been developed in an attempt to maximize adherence, they are little used in the United States, likely related to costs. Because of this, taking 3 to 4 different tablets daily remains the norm, necessitating careful education on potential adverse effects for each component, with an emphasis on the importance of completing the full 14-day course and a review of the rationale for retreatment. Providing anticipatory guidance with a printout of all medications detailing instructions and potential side effects in the patient's native language can be helpful. This practice includes reminding patients not to begin the course of antibiotics until all the medications are amassed and to avoid alcohol consumption while taking metronidazole owing to a potential disulfiram-like reaction.

The financial burden some patients experience is another adherence limitation that should not be overlooked. Although bismuth, amoxicillin, metronidazole and most proton pump inhibitors (PPIs) are inexpensive over the short term, the out-of-pocket cost for tetracycline or rifabutin can run to several hundred dollars. Providers can preemptively call the patient's pharmacy, route antibiotics to a different location given price variations, and use discount codes and coupons, but they should also advise the patient to call their office if the medications are too costly, rather than proceeding with only the affordable components. As a less expensive alternative—doxycycline —has been substituted for tetracycline. However, this results in

significantly lower rates of *H pylori* eradication and is therefore not recommended.[4]

Penicillin Allergy Is Usually Not Real

Amoxicillin is an important component of treatments for refractory *H pylori* infection because resistance to this antibiotic remains uncommon. If a patient who has failed 1 or 2 first-line treatment regimens states that they cannot take penicillin because of an allergy, this statement should be probed further. More than 10% of the U S population believe they are allergic to penicillin, but the vast majority of these "allergic" cases can tolerate amoxicillin in practice.[5] Evaluation of penicillin allergy begins with a detailed clinical history regarding the patient's symptoms and a thorough review of relevant medical records. In many cases, a beta-lactam was tolerated previously without any problem, or the patient describes a reaction that is not allergic in nature, but instead a known side effect of antibiotics (such as nausea, vomiting, or diarrhea) that should not preclude its future use. In practice, providers should have a low threshold to refer patients with possible penicillin allergy to an allergist for skin testing and, if necessary, amoxicillin challenge.

Once a true allergy has been excluded, patients can safely be prescribed an amoxicillin-containing regimen, typically a rifabutin triple therapy.[2] For those few patients with a true penicillin allergy, there are several other regimens to consider that do not contain amoxicillin, but with limited evidence to choose from among them, antibiotic resistance testing should be performed at this juncture.[2]

Antibiotic Sensitivity Testing

The overuse and misuse of clarithromycin, levofloxacin, and metronidazole has contributed to a drastic increase in resistance for these antimicrobials worldwide. The paucity of resistance data in the United States is a major limitation for current national *H pylori* treatment recommendations. Best estimates indicate that resistance rates for clarithromycin, metronidazole and levofloxacin are each now greater than 30% in the United States.[6]

Although antibiotic selection for most infectious agents is guided by sensitivity information and/or regional resistance profile tracking, *H pylori* treatment has, until recently, been largely empiric. However, the landscape is changing at long last with the increasing realization that *H pylori* should be treated like any other infectious disease.[7] When there is uncertainty over which regimen to choose, antimicrobial selection should be tailored according to in vitro testing. Historically, only culture-based testing was possible, which is a cumbersome and time-intensive process given the fastidious properties of *H pylori*; it is also not available widely and usually requires sending gastric biopsies to centralized commercial laboratories under stringent transport conditions, which are not always successful at recovering viable organisms. As an alternative, molecular-based susceptibility testing has been developed using a variety of fluorescent probes, polymerase chain reaction, and/or next-generation sequencing.[8] We have found transporting samples for molecular testing by next-generation sequencing to be simple, with a high overall technical success rate, and with results available within a few days.[9] Testing can also be performed retrospectively using sections from formalin-fixed tissues routinely collected for histopathology[9,10] and can even be done on stool samples.[11]

With susceptibility data in hand, the guessing game should be over. A suitable regimen can now be chosen based on this information along with the patient's history of antibiotic tolerance and affordability. However, despite the inherent logic of susceptibility-based regimen selection, well-designed controlled trials are still needed to prove its superiority over the empiric approach for refractory cases.

Acid Inhibition: PPIs Are Not All the Same, and More Is Usually Better

Gastric acid inhibition has long been recognized as an essential component of *H pylori* eradication therapy. Because *H pylori* enters a replicative stage at neutral pH, it is most susceptible to growth-dependent antibiotics, particularly clarithromycin and amoxicillin, when gastric pH levels are increased and maintained between 6 and 8. Without strong acid inhibition, *H pylori* does not replicate, is less susceptible to antibiotics, and can continue to colonize the human stomach once the antibiotics are discontinued. Acid suppression can also improve the stability and half-life of several antibiotics, and some PPIs have direct antibacterial effects in vitro. Given their importance in *H pylori* treatment regimens, PPI bioavailability should be maximized by ensuring patients take them correctly 30 minutes before eating.[12]

PPI dosing and frequency are also important considerations for sustaining gastric pH levels of >6, particularly because once-daily dosing only achieves this goal about 25% of the time during a 24-hour period.[13] In cases of persistent *H pylori* infection, providers can consider increasing PPIs to a higher dose (such as 40 mg twice daily) and/or schedule dosing more frequently (3 or 4 times daily) to achieve this pH goal.

Among drugs in the PPI class, there is a wide range of potency in terms of acid suppression, owing largely to differing degree of metabolism by hepatic cytochrome p450. Genetic variations in *CYPC219* can contribute to treatment success through impacting PPI metabolism.[14] Esomeprazole and rabeprazole are less influenced by extensive or ultra-rapid metabolism and are, milligram for milligram, more potent than other PPIs[15]; therefore, they may be the best choice in difficult cases, including in regions with high rates of antibiotic resistance.[14] The concept that more acid suppression results in better eradication rates is supported by the promising results obtained with vonoprazan, a potassium-competitive acid secretion inhibitor that provides more profound acid

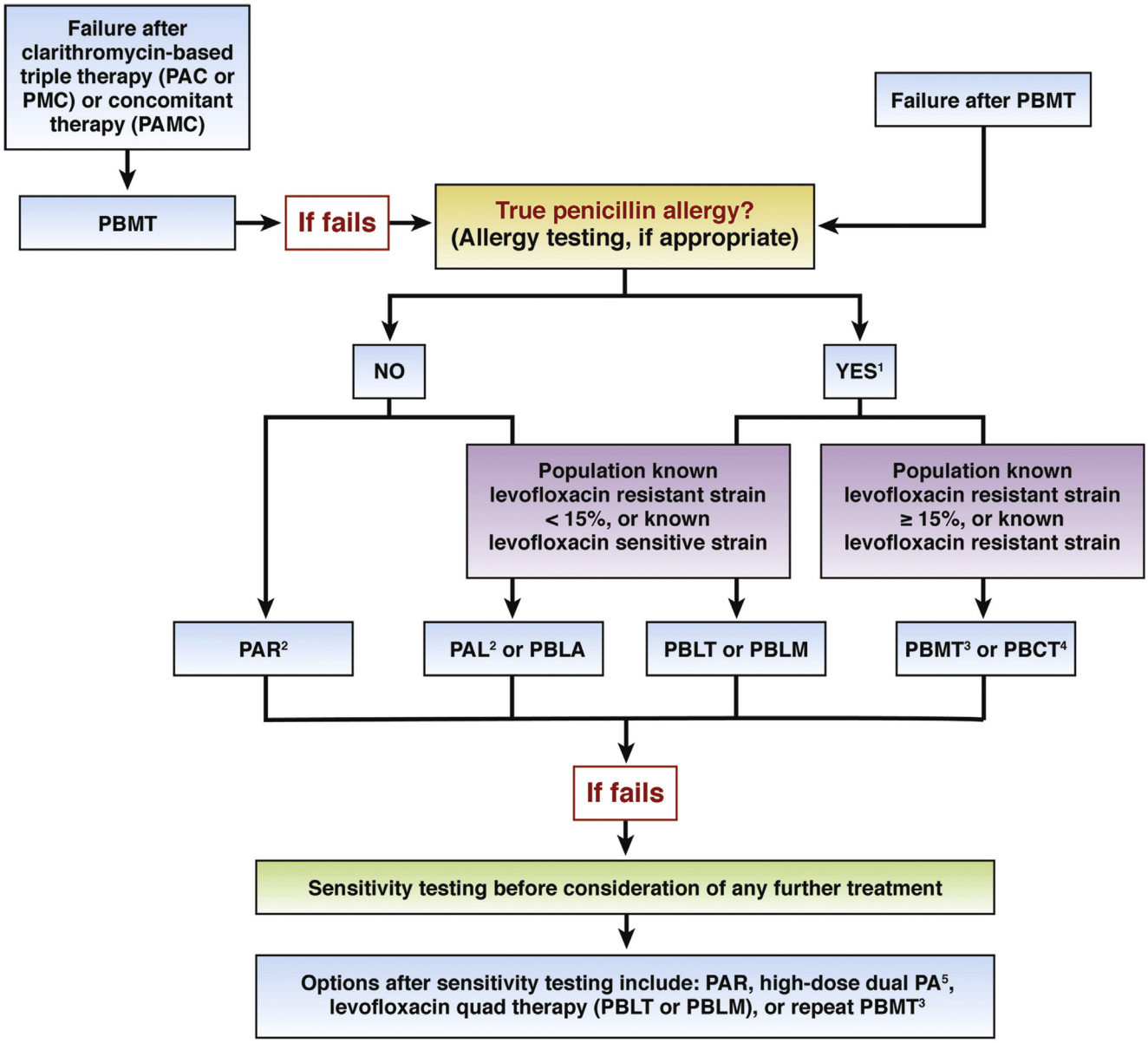

Figure 1. Treatment algorithm for refractory *Helicobacter pylori* infection. Modified from Shah SC, Iyer PG, Moss SF. AGA clinical practice update on the management of refractory *Helicobacter pylori* infection: expert review. Gastroenterology 2021;160:1831–1841. [1]Limited evidence guiding therapy in individuals with true penicillin allergy. [2]With high-dose or high-potency PPI, amoxicillin 750 mg TID. [3]High-dose metronidazole (1.5–2 g divided). [4]Only if clarithromycin sensitive strain. [5]High-dose dual PA = amoxicillin 2–3 g daily in 3–4 divided doses + high-dose PPI BID. PA in place of PAR may be considered, although one study from the US demonstrated superiority of PAR compared to PA as first-line treatment (Graham et al, 2020); however, this has not been directly compared in refractory *H pylori* treatment. A, amoxicillin; B, bismuth; C, clarithromycin; L, levofloxacin; M, metronidazole; P, proton pump inhibitor; R, rifabutin; T, tetracycline.

suppression than traditional PPIs.[16] Although currently not available in the West, studies of vonoprazan in first-line *H pylori* eradication were recently completed in the United States and Europe.[17] Further studies of vonoprazan (and potentially other drugs in this class) are needed to determine whether or not they are superior to PPIs in refractory cases specifically.

Post-treatment Follow-up

The treatment of *H pylori* infection should begin with the intention of confirming eradication ≥4 weeks after an antibiotic course and 2 weeks off PPI therapy. Unfortunately, eradication confirmation remains infrequent in clinical practice. Only 1 in 4 patients are ever retested,[18] and so there are probably many more patients with

difficult to eradicate *H pylori*. There are numerous reasons why retesting rates are low, including transitions in patient care between multiple providers and settings, and the previous advice from older guidelines advising against retesting in most cases (when eradication rates were much higher). We consider the onus on providers who start *H pylori* treatment to then schedule patients for their post-treatment follow-up. That visit provides an opportunity to review symptoms, discuss the importance of determining *H pylori* eradication status, provide reassurance, and offer another antibiotic course if necessary. This practice is particularly important for those ethnic minority groups who are at an increased risk of developing gastric adenocarcinoma and are likely to benefit most from confirmed eradication.[19]

Although a test–treat–prove approach should be adopted for most patients, there are circumstance where the benefit of *H pylori* treatment should be carefully weighed against the risk of repeated antibiotic exposure, including potentially generating multiresistant bacteria or antibiotic-associated complications, such as *Clostridioides difficile*-associated diarrhea. Age, underlying comorbidities, and frailty should also be taken into consideration when making a treatment decision. In cases of persistent *H pylori* infection without evidence of peptic ulcer disease, atrophy, or intestinal metaplasia on endoscopy, providers can consider foregoing further treatments after a careful risk and benefit-centered discussion with the patient. Finally, patients can be reassured that not treating immediately does not mean forgetting, but rather that waiting for better or perhaps simpler regimens to emerge may be wiser, particularly as the absolute gastric cancer risk remains low (1%–3%), and typically takes decades to develop.

Conclusions

The preferred choice for first-line therapy is bismuth-based quadruple consisting of bismuth, metronidazole, tetracycline, and a PPI for 14 days.[20] However, with increasing *H pylori* antimicrobial resistance, most gastroenterologists will need to be competent in also treating refractory cases.

After a failed eradication attempt, the choice of regimen should be tailored to the individual patient, taking into consideration the local antibiotic resistance pattern (if available), cost, antibiotic history, allergies, and the potential profile of side effects. Addressing the nondrug factors that may contribute to eradication failure (such as communication barriers and high drug costs) are also important for treatment success. Furthermore, it should be recalled that the best results in clinical trials have generally been achieved with 14-day courses and strong acid suppression.

Finally, in addition to the general principles for retreating we have outlined in this article, the American Gastroenterological Association's recent clinical practice update on this subject includes an algorithm that can be followed in most cases[2] (Figure 1). When the next choice of therapy is not obvious, resistance testing should be performed, and regimen selection based on the results. With attention to detail, a collaborative patient-based approach, and the use of resistance testing as necessary, *H pylori* can be eradicated in almost all cases.

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