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Treatment Approach of Refractory *Helicobacter pylori Infection*: A Comprehensive Review

Pedro Cortés[1], Alfred D. Nelson[1], Yan Bi[1], Fernando F. Stancampiano[1], Loren P. Murray[1], George G.A. Pujalte[1], Victoria Gomez[1], and Dana M. Harris[1]

Abstract

H. pylori is the most common infection in the world and is associated with gastrointestinal and extra-gastrointestinal manifestations, including peptic ulcer disease, gastrointestinal bleeding, and lymphoproliferative disorders. Despite being discovered less than half a century ago, antibiotic resistance, exacerbated by medication non-adherence and inefficacy of proton pump inhibitors, has grown substantially, explaining the rising incidence of refractory *H. pylori* infection. In this review, we discuss risk factors, treatment options, surveillance and follow-up, as well as emerging therapies for refractory *H. pylori*.

Keywords

H pylori, refractory, treatment, treatment failure, surveillance

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Epidemiology

It is estimated that 50% of the world's population, and 70% to 90% of people in developing countries are colonized with *H. pylori.*[1,2] Refractory infection represents eradication failure and is defined as a positive non-serologic test for *H. pylori* at least 4 weeks after pharmacologic therapy.[3] In contrast, recurrent infection is defined as a positive non-serologic test after an initial negative test following apparently successful eradication therapy.[3] Non-serological tests for *H. pylori* include stool antigen detection, urea breath testing, and gastric biopsies. The distinction between recurrent and refractory *H. pylori* has important therapeutic implications.[3]

Treatment failure is defined as unsuccessful eradication of *H. pylori* as indicated by non-serologic based testing.[3] Approximately 20% to 30% of U.S. patients treated for an initial episode of *H. pylori* fail first-line therapy.[4-6] Eradication becomes harder with each additional course of therapy that fails.[7] Over the years, the eradication rate has fallen to 50% to 75% in some countries,[8-11] which has been attributed to growing antibiotic resistance.[7] Resistance to clarithromycin- and levofloxacin-based therapies has been reported to be between 5% and 25%.[12-14]

In this review article, we outline the approach to testing and treating patients with an initial *H. pylori* infection and refractory cases. We describe the evidence behind treatment recommendations and provide a glimpse of therapies under investigation.

Usual Approach to *H. pylori* Infections

The indications for screening for *H. pylori* include active gastric and duodenal peptic ulcer disease (PUD),[15] new diagnosis of extranodal marginal zone B cell lymphoma,[16] inadequately treated PUD with or without documentation of eradication of *H. pylori*, early gastric cancer or

[1]Mayo Clinic, Jacksonville, FL, USA

Corresponding Author:
Dana M. Harris, Division of Community Internal Medicine, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA.
Email: harris.dana@mayo.edu

gastrointestinal metaplasia resection,[17] and dyspepsia before the age of 60 with no alarm features.[18] Screening should be considered in patients with unexplained iron deficiency anemia, adults with idiopathic thrombocytopenic purpura (ITP), and patients who will be on long-term low dose aspirin, or a non-steroidal anti-inflammatory drug (NSAID).[15]

Non-invasive methods to detect *H. pylori* include ^{13}C or radioactive ^{14}C-urea breath test (UBT), stool antigen detection and serum antibodies. ^{13}C-UBT has the highest sensitivity and specificity (95%),[19] but the stool antigen is the most commonly used in the outpatient setting, with high sensitivity and specificity (94 and 97%, respectively).[20,21] The serologic IgG antibody test has a high negative predictive value but does not help distinguish active from past infection.[2,22] If endoscopy is indicated in the setting of dyspepsia with alarm symptoms and/or gastrointestinal bleeding (GIB), invasive methods such as biopsy for rapid urease test (BRUT), histology, polymerase chain reaction (PCR) and less commonly by bacterial culture are indicated.[23] BRUT is highly specific, but its sensitivity is affected by the number of bacteria.[24] Histological diagnosis also varies with infection burden, location, and pathologist's expertise.[25,26]

Whom to Treat

All patients who test positive for *H. pylori* should be treated.[15] The recommended first-line regimen is based on the patient's history of macrolide or quinolone exposure, presence and type of penicillin allergy, and resistance to clarithromycin and levofloxacin in the geographical area of practice.[15] Areas with high levels of resistance are defined as those with a prevalence of >15% of *H. pylori* strains carrying antibiotic resistance.[15] Treatment regimens must always include a proton pump inhibitor (PPI) and a combination of 2 or 3 antibiotics for 10 to 14 days. At pH 3 to 6, *H. pylori* is in a coccoid form which confers antibiotic resistance; PPIs increase the intragastric pH to 6.0 to 7.0 and susceptibility to antibiotics as it enters its replicative phase.[27]

Recommended First-Line Therapies

In areas where clarithromycin resistance is <15%, recommended first-line treatments are clarithromycin-based triple therapy regimens (PAC, PMC: PPI, amoxicillin plus clarithromycin or metronidazole) for 14 days, to achieve maximum eradication rates.[28] If there is concern for high resistance to clarithromycin or metronidazole, or previous treatment with a macrolide, the recommended treatment is PBMT, bismuth quadruple therapy (PPI, bismuth, metronidazole, tetracycline) for 10 to 14 days.[2,15] If there is only high clarithromycin resistance >15% without prior macrolide use, PAMC (PPI, amoxicillin, metronidazole, clarithromycin) or PBMT should be considered.[22] Only the American College of Gastroenterology (ACG) recommends levofloxacin as a first-line treatment, but given concerns for increasing resistance and decreased efficacy, it is not recommended by other consensus groups.[1,15] Since most patients who report a history of adverse reactions to penicillin are not penicillin-allergic, testing, and delabeling should be attempted. Penicillin-based regimens have been found to yield an eradication rate of 80% to 90%.[3,29]

Treatment After Failure of First-Line Therapy

Resistance to amoxicillin or tetracycline is rarely seen but commonly seen with clarithromycin, metronidazole, and levofloxacin. Retreatment after failed *H. pylori* first-line treatment has an eradication rate of 84% to 87% with a levofloxacin or rifabutin-based regimen, 71% with an amoxicillin-based regimen, and 85% to 90% with PBMT.[29-32] For retreatment or as a second-line regimen, PBMT is recommended, if not previously used; otherwise, a levofloxacin-based regimen for 10 to 14 days is preferable: triple therapy PAL (PPI, levofloxacin, amoxicillin), sequential therapy (PPI and amoxicillin × 5-7 days, then PPI, levofloxacin and metronidazole for 5-7 days) or LOAD (PPI, levofloxacin, doxycline, metronidazole). Other options are amoxicillin-based therapies: sequential (PPI and amoxicillin for 5 days then PPI, clarithromycin, metronidazole for 5 days), high dose HDDT (PPI and amoxicillin high dose) or rifabutin PAR (PPI, amoxicillin, rifabutin). HDDT is efficacious by increasing the pH of high dose PPI which indirectly increases the efficacy of amoxicillin.[33,34] PAR is considered last resort as salvage therapy due to concern for myelosuppression.[35]

Vonoprazan is a potassium-competitive acid blocker approved in Japan for first and second-line *H. pylori* therapy. It is superior to PPIs as first-line therapy and as effective as PPI for second-line therapy.[36] If *H. pylori* infection persisted after treatment with second-line therapy, *H. pylori* cultures along with antibiotic susceptibility testing would be recommended.

Risk Factors for Treatment Failure

Poor adherence and antibiotic resistance are the 2 major risk factors for *H. pylori* eradication failure.[3] Other risk factors include high gastric acidity, high bacterial load, lack of sensitivity of the specific strain of *H. pylori* to antibiotics and lack of provider awareness to local and national resistance patterns for specific antibiotics.[22] Poor adherence may be due to the complexity of the regimen or its adverse effects, drug availability, cost, high pill burden, or lack of patient education regarding the importance of *H. pylori* eradication.[3] Resistance to clarithromycin and levofloxacin leads to treatment failure by 7-fold and 8.2-fold respectively, in

both refractory and treatment-naïve *H pylori* infections and may further increase with previous eradication failure.[37] Across the United States, the rates of resistance to clarithromycin, levofloxacin and metronidazole range between 13% to 17%, up to 29%, and 25% to 44%, respectively, depending on the specific geographical area.[31,38] Pharmacogenomics patterns have been implicated as a risk factor for eradication failure as polymorphisms in the cytochrome P450 enzyme (CYP2C19), interleukin-1, and P-glycoprotein 1 (MDR1) lower the PPI concentration in the stomach, indirectly decreasing the efficacy of amoxicillin and clarithromycin.[3,39,40] Finally, discontinuation of tobacco products should be strongly recommended as smoking nearly doubles the odds of treatment failure.[41]

Evidence-Based Approach to Treatment of Refractory Cases

PBMT, bismuth quadruple therapy, is the only FDA-approved regimen for the treatment of refractory *H. pylori* infection.[3] A prospective study of 227 patients treated with PBMT for refractory *H. pylori* infection showed a superior eradication rate of a 14-day treatment compared to a 7-day course, (93.6% vs. 77.2%).[31] A large retrospective study of 790 patients, treated between 2004 and 2014, confirmed the superiority of a 14-day of PBMT (eradication rate of 84.1%).[30] In a more recent prospective study of 54 patients with refractory *H. pylori* who received PBMT for 7 or 14 days, the authors showed an overall eradication rate of 88.8% and used multivariate-analysis to identify metronidazole-resistance, defined as a minimum-inhibitory concentration (MIC) of greater than 32 μm/mL, as the sole risk factor for eradication failure (eradication rates = 92.8% for MIC 8-32 μm/mL and 60% for MIC > 32 μm/mL).[42] The eradication rate with PBMT is in the 85% to 90% range, when used to treat patients with up to 3 failed episodes, but treatment success deceases to 67% when it is used in a 4th episode of refractory *H. Pylori* infection, as shown in a prospective study of 208 patients with refractory infections who had an adherence rate of 95%.[32]

If PBMT fails and there is no penicillin allergy, the next treatment is PAL provided that levofloxacin resistance is <15% in the local population. In a randomized controlled trial of 160 patients with refractory *H. pylori*, a 10-day course of PAL had a superior eradication rate of 85% when compared to 65.7% for a 7-day course ($P = .004$), suggesting length of therapy played a significant role.[43] In a prospective study of 150 patients, a 10-day course of PAL showed a similar eradication rate of 90% for refractory *H. pylori*.[44] A meta-analysis of 322 studies on levofloxacin-based regimens found resistance played a significant role on the eradication rate of refractory *H. pylori* as the risk ratio for efficacy was 2.18 ($P < .001$) in levofloxacin-susceptible strains when compared to resistant strains, suggesting that levofloxacin should be avoided if resistance is greater than 5% to 10%.[45] To date, there are no head-to-head randomized controlled trials comparing the efficacy of PBMT and PAL in refractory *H. pylori*.

Alternatively, rifabutin-based therapies, (ie, PAR), are recommended when there is no penicillin allergy and levofloxacin resistance is >15% in the local population. In a prospective study of 39 patients with refractory *H. pylori* secondary to clarithromycin- and levofloxacin-resistant strains, a 10-day treatment course of PAR had an eradication rate of 79.5%.[46] A larger prospective study of 302 patients treated with PAR for 14 days showed a similar eradication rate of 72.7% in patients with refractory *H. pylori*.[47] Figure 1. In a more recent study of 19 patients, vonoprazan was used as the acid-suppressant in the PAR regimen in patients with refractory *H. pylori*, demonstrating an eradication rate of 100%.[48]

Following the failure of 2 lines of therapy for refractory *H. pylori*, susceptibility testing for the underlying strain is recommended. The efficacy of culture-guided treatment of *H. pylori* has been widely studied. In a prospective study of 2606 patients with *H. pylori* infection, 58 patients (2.2%), who had failed 2 lines of subsequent therapy, underwent EGD with *H. pylori* culture and were treated with a bismuth-based targeted therapy, which achieved an eradication rate of 77% per-protocol analysis, and 52% via intention-to-treat analysis; there was 56% resistance to clarithromycin and metronidazole/tinidazole, 12% to tetracycline and no resistance to amoxicillin.[49] In a similar study, 94 patients, who had failed 2-lines of subsequent therapy, were treated using a culture-guided approach with a quadruple-based bismuth-based therapy, and achieved an eradication rate of 90%.[50] Again, resistance rates to metronidazole and clarithromycin were high (100% and 95%, respectively) but lower for levofloxacin and tetracycline (31% and 5%, respectively).[50] Multiple cost-effective analyses across different nations have found a culture-guided approach to *H. pylori* eradication to be cost-effective with a savings ranging from $5 to $657 USD per patient.[51-54]

Surveillance and Follow-Up

Gastric cancer is the third most common cause of malignancy-related death in developed countries, and chronic *H. pylori* infection, classified as a type I carcinogen, accounts for up to 89% of non-cardia gastric cancer.[55] The carcinogenesis of *H. pylori* follows a stepwise progression pattern from normal mucosa to non-atrophic gastritis, atrophic gastritis intestinal metaplasia and to gastric cancer.[56] Evidence shows that eradication of *H. pylori* reduces the risk of gastric cancer in infected asymptomatic patients as well as in those individuals with a family history of gastric cancer in first-degree relatives.[57-59] In addition, *H. pylori* infection is associated with marginal zone lymphomas of the mucosa associated lymphoid tissue (MALT) type, a B-cell neoplasm

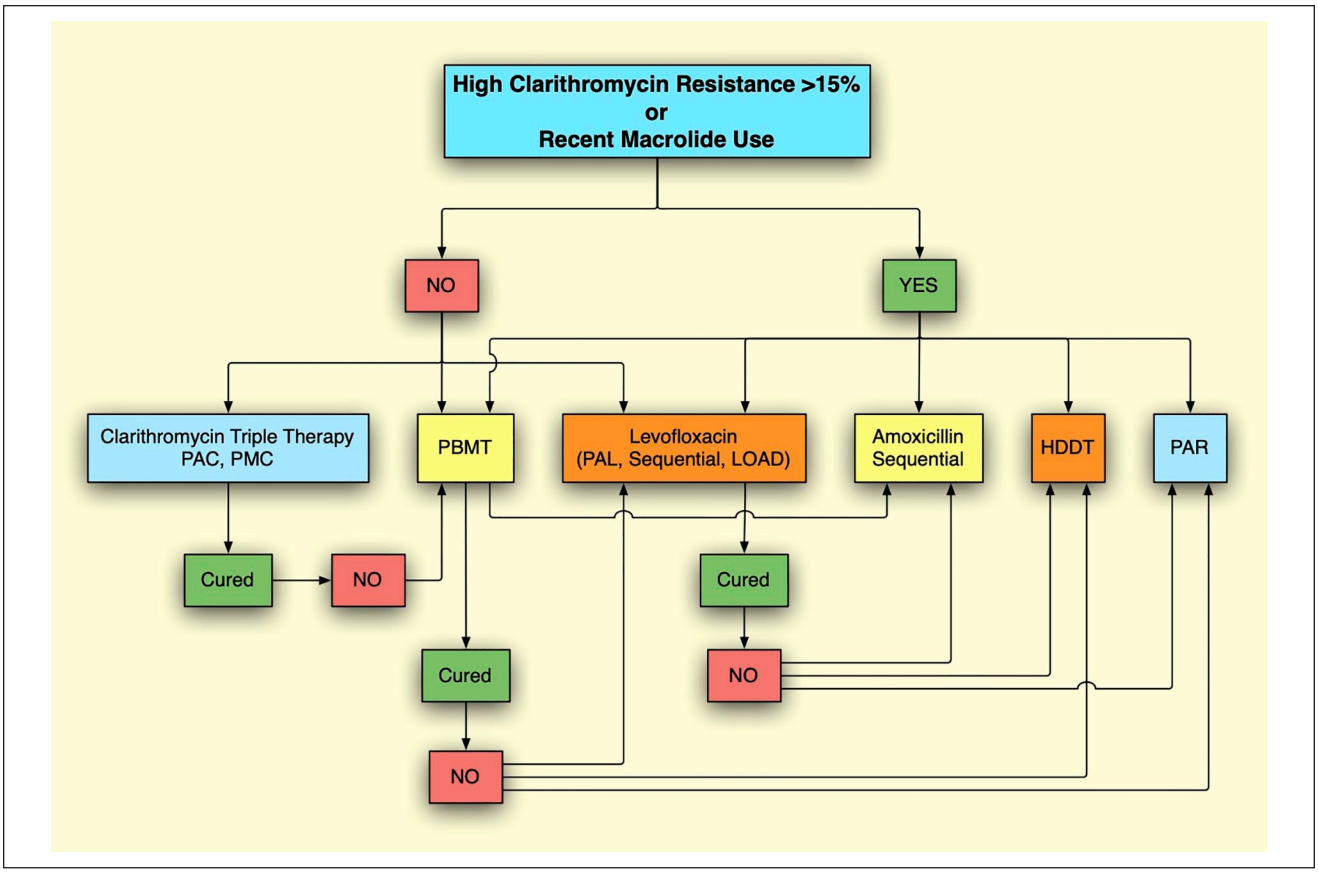

Figure 1. Simplified treatment algorithm for H. pylori infection.

involving lymphoid tissue outside lymph nodes. Due to increased drug resistance of *H. pylori* to current therapy and declining success rate of *H. pylori* eradication therapy, it is recommended to test all infected patients for *H. pylori* eradication after the end of therapy.[60]

For every patient treated for *H. pylori*, testing is recommended with a non-serologic test, preferably non-invasively with UBT or fecal antigen testing. If endoscopy is indicated, gastric biopsy-based testing may be obtained. Testing should be performed 4 weeks after treatment completion.[15] PPI and bismuth-containing medications should be discontinued at least 2 weeks before testing for eradication, as they interfere with the sensitivity of testing.[15] Testing eradication serves to determine treatment success or failure.[15] If testing reveals presence of *H. pylori* and indication of persistent infection despite treatment, the diagnosis is refractory *H. pylori* infection.[3] Testing for eradication in refractory cases follows the same recommendations as for an initial *H. pylori* infection, that is, testing should be performed 4 weeks after treatment.[15] Following eradication of *H. pylori*, serial surveillance testing is not recommended.[15] Patients successfully treated may still be at risk for future gastric cancer development if they are found to have advanced gastric atrophy or intestinal metaplasia. These patients should be evaluated with surveillance endoscopy based on their ethnicity and family history for gastric cancer screening.[61]

Horizons

The potassium-competitive acid blocker vonoprazan is more potent than conventional PPIs at suppressing intragastric acid and CYP2C19-independent metabolism.[36] Vonoprazan-based therapy with amoxicillin is effective, resulting in eradication rates of 85% to 89%. Vonoprazan is only approved in Japan as both first- and second-line therapies.[36] Antibiotic susceptibility testing has been advocated by the Maastricht expert consensus group since the inception of *H. Pylori* guidelines in 1997.[62] It is not widely available for use in clinical practice due to cost and a cumbersome and labor-intensive process.[3] Alternatively, molecule resistance testing, which is becoming more widely available, is simpler to use and decreases the need for specialized tissue handling.[62]

Conclusion

Refractory *H. pylori* is becoming a growing concern for patients and healthcare providers given its increasing prevalence and difficulty in treating. Refractory *H. pylori* is present when there has been treatment failure, defined as a positive non-serologic test at least 4 weeks following a treatment attempt. The most widely used regimen for refractory *H. pylori* is PBMT, which has eradication rates of 85% to 90%. If PBMT fails, local metronidazole-resistance likely played a role. Culture-driven therapy is a cost-effective approach for refractory *H. pylori and* is indicated after 2 treatment failures, but availability may be a problem. Molecular testing for clarithromycin resistance is an emerging testing modality and, in the future, may include testing for other antibiotics. Emerging therapies for refractory *H. pylori* include pharmacogenomics to guide PPI use and the use of new molecules like vonoprazan.

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ORCID iDs

Pedro Cortés https://orcid.org/0000-0002-2505-2283
Fernando F. Stancampiano https://orcid.org/0000-0002-9162-1632
Dana M. Harris https://orcid.org/0000-0003-0820-9215

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