Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Helicobacter pylori Treatment***
-January 2023-

Background:

At the 2023 Winter meeting, the National Pharmacy and Therapeutics Committee (NPTC) reviewed the current available initial and refractory treatment options for *Helicobacter pylori (H. pylori)* infection, as well as guidelines for the treatment of *H. pylori*, to determine if changes to the National Core Formulary (NCF) were warranted. The NCF currently lists antibiotics indicated in *H. pylori* treatment including amoxicillin, doxycycline, and metronidazole as well as "any" Proton Pump Inhibitor (PPI). Following the NPTC clinical and pharmacoeconomic review and analyses, the NPTC voted to **ADD bismuth subsalicylate** to the NCF.

Discussion:

H. pylori is a gram-negative bacterium transmitted through the fecal-oral route. *H. pylori* infection occurs when *H. pylori* bacteria infect the stomach or gastrointestinal tract. It can cause peptic ulcer disease and lead to gastric cancers.[1] Within North America, the prevalence of infection is higher in socially disadvantaged people who have immigrated to North America and in certain racial and ethnic groups, including African Americans, Hispanic Americans, American Indians and Alaska Natives.[2]

Among Navajo adults in Arizona, the *H. pylori* prevalence is 62%, while 75% of the Alaska Native population are reportedly infected with *H. pylori*. Rural Alaska Native patients have the highest rates of treatment failure compared to urban Alaska Native patients and urban non-Native patients, and this population is two to four times more likely to develop gastric cancer vs. the U.S. Caucasian population. Alaska Natives living in rural villages who were previously treated successfully have a 22% two-year reinfection rate. The Navajo Epidemiology Center reported the age-adjusted incidence rate of gastric cancer among members of the Navajo Nation as 14.2 per 100,000, which is nearly four times higher than among the non-Hispanic Caucasian population in AZ.[3-8]

Reasons for initial *H. pylori* treatment failure include poor adherence to medication regimens due to duration and complexity, as well as antibiotic resistance. The *H. pylori* eradication rate with PPI-based triple therapy has fallen from >90% in the 1990s to <70% currently. The U.S. Centers for Disease Control and Prevention Arctic Investigations Program *H. pylori* sentinel surveillance program includes four referral medical centers in Alaska. Between 2000 and 2016, the surveillance system received 2868 specimens, of which 1177 were confirmed positive for *H. pylori*. Specimens that originated from the same patients within the same year were excluded, yielding 800 *H. pylori* isolates. More than one-half of the *H. pylori* isolates (456/800; 57.0%) were resistant to at least one of the antimicrobial agents tested. Metronidazole resistance was most common (342/800; 42.8%), followed by clarithromycin resistance (238/800; 29.8%). Co-resistance to clarithromycin and metronidazole was also present (128/800; 16.0%).[9]

Indications for H. pylori testing include active peptic ulcer disease (PUD), past history of PUD (unless previous cure of *H. pylori* infection has been documented), low-grade gastric mucosa associated lymphoid tissue lymphoma, and a history of endoscopic resection of early gastric cancer. Those who test positive should be offered treatment for the infection. Per the 2017 American College of Gastroenterology guidelines, there are 8 first-line treatment regimens for *H. pylori* infection. These initial treatment regimens include:[2]

- Clarithromycin Triple Therapy with either amoxicillin or metronidazole (14 days)
- Bismuth Quadruple Therapy (10-14 days)
- Non-Bismuth Quadruple Therapy/ Concomitant therapy (10-14 days)
- Sequential Therapy (5-7 days each for 10-14 day total duration)
- Levofloxacin Triple Therapy (10-14 days)
- Hybrid therapy (7 days each for 14 day total duration)
- Levofloxacin Sequential Therapy (5-7 days each for 10-14 day total duration)
- LOAD therapy with doxycycline (7-10 days)

When selecting a first-line treatment regimen, the clinician should assess the patient's history for penicillin allergy, as well as assessing for prior macrolide exposure for any reason, local clarithromycin resistance rates $\geq$ 15%, and/or local eradication rates with clarithromycin-based triple therapy $\leq$85%. Testing for eradication should be performed at least 4 weeks after the completion of antibiotic therapy and after PPI therapy has been withheld for 1-2 weeks. Eradication testing should be performed using a urea breath test, fecal antigen test, or biopsy-based testing. When performed properly, all three tests are highly sensitive and specific at detecting persistent *H. pylori*. The choice of test should be individualized to patient variables such as availability, cost, etc.[2]

If *H. pylori* infection persists, every effort should be made to avoid antibiotics that have been previously taken. In patients with persistent *H. pylori* infection, perform culture and sensitivity to guide antibiotic treatment, if available. The selection of a salvage regimen should be directed by local antimicrobial resistance data and patient's previous antibiotic exposure. If the initial treatment contained clarithromycin, the refractory treatment should include either bismuth quadruple therapy or a levofloxacin salvage regimen. If bismuth quadruple therapy was used for initial treatment, clarithromycin- or levofloxacin-containing salvage regimens should be used. However, clarithromycin triple therapy should be avoided as a salvage regimen.[2]

Although not yet commercially available on the U.S. market, potassium-competitive acid blockers (P-CABs) with antimicrobial combination treatments have been shown to be superior or non-inferior to conventional PPI-based triple therapies for first- and second-line treatment, and superior in patients with evidence of antimicrobial resistant infections. The first P-CAB was approved in the U.S. in May 2022 for *H. pylori* eradication when used with amoxicillin and/or clarithromycin. Vonoprazan is the first-in-class P-CAB agent.[10]

Vonoprazan triple and dual therapy for *H. pylori* infection: A phase III, randomized clinical trial (RCT) included 1406 treatment naïve adults with *H. pylori* infection in the U.S. and Europe. Participants received treatment with either vonoprazan 20mg (as double therapy with amoxicillin 1g or triple therapy with amoxicillin 1g) and clarithromycin 500mg and were compared to patients receiving lansoprazole 30mg (triple therapy) with amoxicillin 1g and clarithromycin 500mg. In all patients, vonoprazan dual and triple therapy were superior to lansoprazole triple therapy (80.8% and 77.2% respectively, vs. 68.5%, difference 12.3%; 95% CI, 5.7-18.8; $p<0.001$; difference 8.7%; 95% CI, 1.9-15.4; $p=0.013$) with no marked difference in adverse events in each treatment group.[11]

Vonoprazan as a component of first-line and second-line triple therapy for *H. pylori* eradication: A phase III, double-blind RCT was conducted at 46 sites in Japan which included 650 *H. pylori* positive adult patients with gastric or duodenal ulcer history. Treatment regimens included vonoprazan 20mg triple therapy with amoxicillin 750mg and clarithromycin 200mg or 400mg vs. lansoprazole 30mg triple therapy with amoxicillin 750mg and clarithromycin 200mg or 400mg. The eradication rate with vonoprazan was 92.6% (95% CI: 89.2% to 95.2%) compared to 75.9% (95% CI: 70.9% to 80.5%) with lansoprazole; a difference of 16.7% thus confirming non-inferiority ($p<0.0001$).[12]

Recently updated International guidelines show trends moving away from clarithromycin triple therapy regimens unless antibiotic resistance testing is completed prior to therapy initiation. In countries with P-CAB therapy availability, treatment success rates increased with the use of P-CAB therapy. Per the American College of Gastroenterology, an update is currently in progress for *H. pylori* infection guidelines but no release date is noted.

Findings:

All classes of agents or specific agents used in the treatment of *H. pylori* infection were reviewed for availability on the NCF. Evidence from published literature, guidelines, and internal pharmacoeconomic analyses offers a value-based decision opportunity, which supports the addition of bismuth subsalicylate to the NCF.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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