Management of Resistant *Helicobacter Pylori* Infection

BACKGROUND

Helicobacter pylori (*H. pylori*) infection affects over 50% of the population worldwide.[1] This equates to 4.4 billion people throughout the world and over 100 million in the United States.[1,2] Each year, approximately 2.5 million patients in the United States seek treatment for *H. pylori* infection.[1]

The International Agency for Research on Cancer (IARC) has classified *H. pylori* as a group 1 carcinogen.[1] Patients with *H. pylori* infection are at an increased risk for the development of peptic ulcer disease, gastritis, and non-cardiac gastric cancer.[1] Gastric cancer is the second most common cause of cancer deaths worldwide.[3]

H. pylori was discovered in 1982.[4] By 1994, the National Institutes of Health stated that *H. pylori* infection was the cause of most recurrent duodenal and gastric ulcers and IARC had classified *H. pylori* as a group 1 human carcinogen for gastric adenocarcinoma.[4] The prevalence of *H. pylori* infection, along with the widespread use of antibiotics, has caused a growing problem of infections that are resistant to the standard treatment regimens.[1] Recently, the World Health Organization (WHO) declared that there is an urgent need to develop new treatments for clarithromycin-resistant *H. pylori.*[1]

Clarithromycin-based treatment regimens have previously been the standard for eradication of *H. pylori* infection. However, clarithromycin currently fails to eliminate *H. pylori* in 25% to 40% of all cases.[5] *H. pylori* resistance to clarithromycin has more than doubled between 2009 and 2013.[5] This may be primarily due to the overuse of clarithromycin in upper respiratory infections.[6] Other standard treatments include metronidazole or levofloxacin. Unfortunately, resistance to both antibiotics is also high.[6]

On November 4, 2019, Redhill Biopharma announced FDA approval of combination omeprazole magnesium, amoxicillin, and rifabutin, a new treatment option for adults with *H. Pylori* infection.[7] This fixed-dose formulation is the first rifabutin-based therapy for *H. pylori*.[7] In two separate phase 3 studies, this combination treatment demonstrated an 84% eradication rate for *H. pylori* infection with no resistance seen.[1]

EDUCATIONAL ANALYSIS

Gap #1: Clinicians may be unaware of how to choose the correct treatment regimen for *H. pylori* infection

Learning Objective #1: Identify the correct *H. pylori* treatment based on patient's previous antibiotic exposure

"Treatment of *H. pylori* infection has become increasingly difficult due to growing bacterial resistance and the lack of advances in treatment options over the past decade," explained Colin Howden, MD, Chief of Gastroenterology at University of Tennessee Health Science Center in Memphis.[5] Current standard treatments for *H. pylori* eradication in adults include triple therapies, bismuth-free therapies,

and bismuth based quadruple therapy.[8] Choosing the correct treatment regimen should be based on a number of important factors. Clinicians need to consider availability of the particular treatment, the local pattern of primary antibiotic resistance, and cost.[8] Resistance to antimicrobial treatment can be due to either consumption in the general population or previous antibiotic use in individual patients.[8]

In November 2018, Alessia Savoldi and colleagues analyzed 178 studies from 65 countries that assessed *H. pylori* resistance rates to treatment with clarithromycin, metronidazole, levofloxacin, amoxicillin, or tetracycline.[2] The authors concluded that in most regions, resistance of *H. pylori* to these antibiotics was higher than 15%.[2] In those areas where antimicrobial resistance is >15%, another treatment option needs to be chosen.[8] The most favorable treatment in these cases would be a bismuth-based quadruple therapy.[8] This treatment regimen includes bismuth 120 mg, metronidazole 250 mg, and tetracycline 250 mg 4 times daily along with omeprazole 20 mg twice daily for a total of 14 days.[9]

Once local patterns of resistance have been taken into consideration, the clinician should then focus on which treatment to choose for each specific patient. According to Dr Colin Howden, clinicians should ask each individual patient 2 questions before choosing a treatment regimen.[10] The first is whether the patient has had previous exposure to a macrolide antibiotic such as clarithromycin. The second question is whether the patient is allergic to penicillin.[10]

If a patient has been previously exposed to a macrolide, clinicians should avoid clarithromycin treatment. As long as the patient is not allergic to penicillin, bismuth quadruple therapy—as outlined above—should be used.[10]

In cases where there is no history of macrolide exposure and no penicillin allergy, either bismuth quadruple therapy or concomitant therapy are good choices.[10] Concomitant therapy includes clarithromycin 500 mg, amoxicillin 1000 mg, tinidazole 500 mg, and a protein pump inhibitor twice a day for 14 days.[8]

If a patient is allergic to penicillin but has no previous exposure to macrolides, then clinicians may use either bismuth quadruple therapy or clarithromycin triple therapy but replace the amoxicillin with metronidazole.[10] This treatment would include clarithromycin 500 mg, tinidazole 500 mg, and a protein pump inhibitor twice a day for 14 days.[8]

For those patients who are both allergic to penicillin and have been previously exposed to a macrolide, bismuth quadruple therapy is the only option.[10]

Gap #2: Clinicians may be unaware of new treatment options for treatment of resistant *H. pylori* infection in adults

Learning Objective #2: Identify eligible patients for treatment with omeprazole, amoxicillin, and rifabutin

The FDA has recently approved combination omeprazole magnesium, amoxicillin, and rifabutin, as a new treatment option for *H. pylori* resistant infection in adults.[5] This fixed-dose combination therapy is expected to launch in the first quarter of 2020. Each capsule contains amoxicillin 250 mg, omeprazole 10 mg, and rifabutin 12.5 mg.[11] Patients are to take 4 capsules every 8 hours, with food, for 14 days.[11]

Rifabutin is a rifamycin antibiotic that works by inhibiting DNA-dependent RNA polymerase. When combined with omeprazole (a protein pump inhibitor) and amoxicillin (a penicillin-class antibiotic), it demonstrates a high efficacy in eradication of *H. pylori*.[1]

According to David Graham, MD, professor of medicine, molecular virology, and microbiology at Baylor College of Medicine in Houston, TX, "[it] offers patients a much-needed new treatment option for *H. pylori* with an excellent safety and efficacy profile that is not compromised by clarithromycin or metronidazole resistance."[5] The efficacy and safety profile of the combination was demonstrated in two phase 3 studies. Only 1% (4 of 305 patients) treated with the new regimen stopped treatment due to an adverse drug reaction. These adverse reactions included nausea and vomiting, nasal congestion, and nasopharyngitis.[5]

In a randomized, double-blind, controlled study of 455 *H. pylori* positive adults, the new formulation had an 83.8% eradication rate compared with 57.7% in those patients treated with control (P <0.0001).[12] A second placebo- controlled study supported these results. In this study, patients on the new regimen had a 76.6% (95% CI: 66.0%, 84.7%) eradication rate vs 2.4% for placebo treated patients.[12]

The new treatment should not be used in patients with a GFR <30ml/min or those with hepatic impairment.[11] It is contraindicated for use in patients concomitantly using rilpivirine, delavirdine, or voriconazole.[7] The most common adverse reactions (>=1%) include diarrhea, headache, nausea, abdominal pain, chromaturia, rash, dyspepsia, oropharyngeal pain, vomiting, and vulvovaginal candidiasis.[7]

The safety and efficacy of this new formulation offers hope for the future eradication of *H. pylori* infection. "[it] offers a new effective treatment option to overcome bacterial resistance and provide optimal efficacy and I believe it could become a recommended first-line standard-of-care treatment for *H. pylori* infection," said Dr Colin Howden.[5]

SUGGESTED FACULTY LIST

1. Colin Howden, MD, Professor of Medicine and Chief, Division of Gastroenterology, University of Tennessee Health Science Center, Memphis, TN
2. David Y Graham, MD, Professor of Medicine, Molecular Virology, and Microbiology, Baylor College of Medicine, Houston, TX

CONCLUSION

H. pylori is a pathogen that has demonstrated high resistance to current standard therapies. Eradication of *H. pylori* infection is crucial for the prevention of gastric cancer.[3] When infection is caught and treated early, gastric damage can be reversed.[4] With current eradication rates at less than 80% due to antibiotic resistance, it is critical for clinicians to choose the correct treatment regimen to optimize the patient's chance for successful elimination of *H. pylori* infection.

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