CLINICAL VIGNETTE

Salvaging the Salvage Regimen – A Difficult Case of Helicobacter pylori Gastritis

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Introduction

Chronic gastritis due to Helicobacter pylori is a common problem world-wide. Prevalence rates are highest in the developing world, though it remains a significant problem in developed settings with one study finding a seroprevalence rate of 32.5% in surveyed adults in the United States.[1] H. pylori infection has been associated with multiple diseases in addition to chronic gastritis including gastric and duodenal ulcers, gastric adenocarcinoma, MALT-lymphoma, and is even a potential cause of chronic urticaria. Cases are often brought to medical attention as part of evaluation of abdominal symptoms. Treatment involves multidrug therapy according to established regimens; however, treatment failure continues to be a problem. Though algorithms guide clinicians through first line, second line, and salvage therapies, the optimal management of cases refractory to salvage regimens is not yet known. Here is a case of successful salvage treatment using a modified high dose dual therapy regimen.

Case

A 68-year-old non-smoking man with type 2 diabetes, hypothyroidism, hyperlipidemia, and hypertension, was seen in ID clinic for evaluation of persistent H. pylori infection. He was initially diagnosed with H. pylori gastritis in the setting of chronic epigastric pain and nausea that led to EGD with gastric biopsies demonstrating chronic H. pylori gastritis. After initial diagnosis he was first treated with a 14-day oral course of amoxicillin 1g BID, clarithromycin 500mg BID, and omeprazole 20mg BID. Due to persistent detection of stool antigen he was retreated with an oral course of amoxicillin 1g BID, clarithromycin 500mg BID, metronidazole 500mg BID, plus omeprazole 20mg BID for 14 days but was unable to fully comply and missed many doses of the regimen. Repeat stool antigen testing revealed persistent infection. He was then started on a third oral regimen with amoxicillin 1g BID, levofloxacin 250mg PO BID, plus omeprazole 20mg BID for 14 days and reported full compliance, however, he continued to test positive by stool antigen. At that point, then over one year after initial diagnosis and with ongoing abdominal symptoms, he was referred to ID clinic for evaluation of refractory disease. EGD for culture was advised, with H. pylori isolated and susceptible only to amoxicillin and tetracycline. He was started on an oral salvage regimen with amoxicillin 1g TID, doxycycline 100mg BID, bismuth 524mg BID, and omeprazole 20mg BID for 14 days. Subsequent H. pylori stool antigen testing remained positive. At that point the decision was made to add high dose oral bismuth 524mg QID to a modified high dose dual therapy oral regimen of amoxicillin 750mg QID and omeprazole 40mg TID for 14 days. Subsequent H. pylori testing approximately two months later was negative and the patient was satisfied having overall significant improvement in his symptoms compared to before treatment.

Discussion

As demonstrated with this case, the treatment of H. pylori is not always straightforward. Factors such as poor compliance, allergies, drug intolerance, resistant organisms, low gastric pH, and high bacterial burden are all suspected factors for causing refractory disease and decreased rates of eradication.[2] However, when clinically significant H. pylori infection is identified, treatment is generally recommended until eradication is achieved, both for symptomatic benefit as well as reducing the risk of long-term sequela of infection such as gastric malignancy.

Current guidelines implement a multi-drug approach usually including two antimicrobials and a proton pump inhibitor (PPI) to raise gastric pH which increases the efficacy of the antibacterial agents. More recent data suggest the need to use higher antimicrobial doses given for longer durations, with guidelines now favoring 14 days of therapy for most regimens.[3,4] Adjunctive agents such as statins and probiotics have not yet been confirmed to have a significant clinical role in H. pylori management.

The standard approach is to initially treat with a multi-drug regimen such as quadruple therapy with bismuth, tetracycline, metronidazole, and a PPI or triple therapy with clarithromycin, either amoxicillin or metronidazole, and a PPI.[4] Salvage regimens include triple therapy with levofloxacin (or rifabutin), amoxicillin, and a PPI, or quadruple therapy with bismuth, clarithromycin, tetracycline, and a PPI, or high dose dual therapy with amoxicillin and a high dose PPI.[5] There remains lack of consensus as to the best regimen for salvage therapy.

Confirmation of eradication should be performed at least four weeks after treatment and while off the PPI for at least two weeks in order to avoid a false negative.[6] After failure of two treatment courses, an attempt at gastric biopsy should be considered to culture the organism for susceptibility testing. If obtaining cultures is not successful or possible, a regimen

should be selected avoiding antibiotics to which the patient was previously exposed. However, H. pylori rarely develops resistance to amoxicillin, tetracyclines, or bismuth which can therefore be considered in salvage regimens.[5]

Low rates of resistance make regimens combining amoxicillin and tetracyclines attractive for salvage therapy, however, the overall efficacy or superiority to other regimens is not clear and concern is raised regarding their antagonistic pharmacodynamics.[7,8] The low rate of resistance and the good bactericidal activity of bismuth makes it an attractive agent commonly used in salvage regimens.[9,10] Interestingly, despite amoxicillin and bismuth retaining efficacy against refractory H. pylori, trials have shown mixed results regarding their combined use.[11,12] The patient in this vignette was ultimately successfully treated by adding bismuth to a modified high dose dual therapy regimen with the goal of a synergistic effect between bactericidal amoxicillin and bismuth alongside high dose omeprazole.

After apparent cure, it is important to monitor for any recurrent symptoms which if present should prompt re-evaluation for active H. pylori. One cause of recurrent disease is reinfection, although this is thought to be less common in developed settings. Another and possibly more common cause is recrudescent disease of prior infection that was suppressed rather than eradicated.[13] Once true eradication is achieved, patients may experience several benefits including improvement in their dyspeptic symptoms as well as decreased rates of gastric cancer.[14] Such benefits provide strong motivation to press forward with treatment even in refractory cases.

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