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ID TEACHING CASES

Successful Suppression of Drug-Resistant *Helicobacter pylori* Infection With Bismuth Subsalicylate

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We report a case of a 67-year-old female with *Helicobacter pylori* gastritis who experienced continued symptoms as well as persistently positive breath tests and gastrointestinal biopsy results despite multiple courses of evidence-based targeted antibiotic therapies. A trial of suppressive bismuth subsalicylate monotherapy resulted in significant clinical improvement, and repeat gastric and duodenal biopsies were negative for *H. pylori* in the setting of suppressive bismuth treatment. Given the ubiquity of this infection worldwide and its association with abdominal discomfort, indigestion, ulcerative disease, and malignancy, this report highlights an under-reported treatment modality that can greatly improve symptoms and suppress infection, though continued screening is needed in such cases given the suppressive rather than eradicative mechanism of therapy.

Helicobacter pylori is a spiral-shaped, catalase-, oxidase-, and urease-positive, gram-negative flagellated bacterium infecting ~50% of the world population [1]. Common gastrointestinal issues associated with *H. pylori* include chronic gastritis, ulcerative disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [2]. Given the carcinogenic effects of this common bacterium, accurate diagnosis and treatment are crucial. Treatment is intended to be eradicative, with multiple evidence-based targeted antibiotic regimens available. Selection of a specific treatment regimen should consider the local antibiogram as well as susceptibility data of the specific strain of bacteria if available to achieve high cure rates. However, in many cases, it is difficult to eradicate the organism despite multiple courses of antibiotic therapy. We report a case of treatment-resistant *H. pylori* with bismuth subsalicylate suppressive therapy resulting in undetectable *H. pylori* burden in gastric specimens and alleviated symptomatology.

CASE REPORT

A 67-year-old female developed postprandial epigastric pain and bloating in March 2015. She had no alarm symptoms such as dysphagia, weight loss, or anemia. She had no family history of gastrointestinal cancer and never used tobacco, alcohol, or illicit drugs. At that time, she was not taking nonsteroidal anti-inflammatory medications, H2 blockers, or proton pump inhibitors. Laboratory workup was notable for normal complete blood counts and complete metabolic panel, as well as a positive breath test for *H. pylori*. Treatment was initiated with triple therapy (amoxicillin 1000 mg twice daily, clarithromycin 250 mg twice daily, lansoprazole 30 mg once daily) for 7 days. She had continued symptoms despite compliance with the antibiotic regimen, and thus an upper endoscopy with biopsies was performed, revealing the presence of *H. pylori*. Subsequently, she was treated with 10-day sequential therapy of lansoprazole 15 mg twice daily, amoxicillin 1000 mg twice daily for the first 5 days followed by lansoprazole 15 mg twice daily, clarithromycin 500 mg twice daily, and metronidazole 500 mg twice daily for the next 5 days. Nonetheless, repeat *H. pylori* breath testing was positive a month later, leading to a course of LOAD (levofloxacin 500 mg daily, omeprazole 20 mg daily, nitazoxanide 500 mg twice daily, doxycycline 100 mg twice daily) therapy for 10 days, which again proved unsuccessful. The patient reported compliance and adherence to the treatment regimens, and her family members corroborated the fact that she took all the medications each time as prescribed. Due to failure to eradicate the bacteria despite multiple drug therapies, she underwent immunologic testing including measurements of her immunoglobulin levels as well as CD4 and CD8 cell counts, all of which were found to be normal. Two additional attempts with omeprazole 20 mg twice daily, levofloxacin 250 mg twice daily, and amoxicillin 1000 mg

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twice daily for 10 days as well as a 10-day course of rifabutin 300 mg daily, omeprazole 20 mg twice daily, and amoxicillin 1000 mg twice daily, were unsuccessful, with repeatedly positive breath tests as well as persistent symptoms.

Due to concern for a multidrug-resistant strain of *H. pylori*, she underwent repeat upper endoscopy in March 2017 with biopsies taken for culture and antibiotic sensitivities. Pathology revealed *H. pylori* with cultures showing that the strain was indeed resistant to clarithromycin (Table 1). Based on this new information, therapy that included bismuth subsalicylate 300 mg 4 times a day, tetracycline 500 mg 4 times a day, metronidazole 250 mg 4 times a day, and omeprazole 20 mg twice daily was prescribed for 14 days. A breath test done 4 weeks after completion of this regimen was again positive for *H. pylori*. Subsequently, modified LOAD therapy with moxifloxacin 400 mg daily, pantoprazole 40 mg daily, nitazoxanide 500 mg twice daily, and doxycycline 100 mg twice daily for 10 days was implemented. Moxifloxacin was chosen instead of levofloxacin due to prior exposure to levofloxacin in the recent months in attempts to treat the *H. pylori* with the standard LOAD regimen. A breath test was again positive 6 weeks after completion of the above regimen.

Given failure to eradicate *H. pylori* with 7 different antibiotic regimens despite adherence to treatment, suppressive therapy with bismuth subsalicylate 262 mg, 2 chewable caplets twice a day as monotherapy, was initiated. After 2 months on bismuth subsalicylate therapy, the patient reported marked improvement in her abdominal discomfort, bloating, and overall quality of life. An *H. pylori* breath test done 4 months after starting bismuth subsalicylate therapy was negative. An upper endoscopy in April 2018, 6 months after starting bismuth therapy, showed chemical gastropathy on pathology but did not grow *H. pylori* organisms from the gastric antrum, body, or fundus. After being on bismuth therapy for another 6 months and feeling much better overall, the patient discontinued therapy to assess if the *H. pylori* was truly eradicated or just suppressed. An upper endoscopy with gastric mapping biopsies done 6 months after she stopped bismuth therapy showed recurrence of *H. pylori* in the gastric specimens, though she remained asymptomatic. As such, while resumption of therapy with bismuth was recommended to prevent potential downstream effects of *H. pylori* infection, after a prolonged discussion regarding the risks and benefits associated with restarting therapy, the patient decided to continue to hold off on further treatment as her symptoms had resolved completely. The patient has been off bismuth therapy for 2 years and has remained symptom free.

Table 1. Antibiogram of the minimum inhibitory concentration (MIC) of a multidrug resistant strain of H. pylori

Antibiotic Susceptibility	MIC, mcg/mL
Amoxicillin	0.125
Clarithromycin	>256 (R)
Metronidazole	1
Tetracycline	0.032

Abbreviations: MIC, minimum inhibitory concentration; R, resistance.

DISCUSSION

In the early 1990s, standard triple therapy with a macrolide, amoxicillin, and a proton pump inhibitor for *H. pylori* infection was >90% effective in eradication [3]. However, over the past few decades, triple therapy has declined in efficacy, mainly due to development of macrolide resistance. To minimize development of further resistance patterns, it is important to review a patient's prior antibiotic use, which may predict clarithromycin resistance. As with all bacterial infections, compliance and completion of the prescribed duration of antibiotic therapy are important from an antibiotic stewardship perspective.

H. pylori is reportedly most transcriptionally active at a neutral pH despite its affinity for the acidic environment of the stomach and proximal small intestine. The organism can generate a less acidic environment in the stomach via the effects of its urease enzyme [4]. Because most antibiotics used to treat *H. pylori* depend on active bacterial replication for their effects, proton pump inhibitors, which act to further increase gastric pH, are prescribed concurrently in *H. pylori* treatment cocktails. However, a new form of phenotypic resistance developed by *H. pylori* has resulted in strains that do not only replicate at a neutral pH, and, as a result, the strains are not sufficiently killed by routine antibiotic therapy [4]. This mechanism of resistance is just one of many creative ways *H. pylori* has evaded eradication, and it is highlighted here as an example rather than a definitive explanation for our patient. Medication noncompliance could be another explanation for our patient's treatment-resistant infection, though from our perspective this is extremely unlikely, as she was very motivated to improve her symptoms and quality of life. While the successive therapies may not be exactly as the current guidelines advise, the patient's initial treatment journey began in 2014 when the treatment guidelines were different. Moreover, she had some limiting factors preventing her from taking only guideline-based therapies including costs. As clinicians, we also recognize that often after a patient has failed multiple regimens, there is not clear guidance on what to do next. Ultimately, it was the initiation of bismuth subsalicylate monotherapy that provided the most clinical improvement for this patient. While the bismuth-based quadruple therapy failed in this patient, likely due to the short course of bismuth in the regimen, the prolonged course of bismuth monotherapy has successfully kept her disease suppressed. As such, one can infer that while the bismuth was not curative as part of a short course of therapy, it can be used to suppress *H. pylori* in patients who fail treatment regimens that include this agent.

Bismuth is commonly employed in combination therapy for treatment of *H. pylori*, but it is infrequently used as monotherapy. The exact mechanism of action of bismuth is unclear, but it has been shown to inhibit adenosine triphosphate production in *H. pylori* and exhibit bactericidal activity [5, 6]. As with our patient, the current literature describes patients who were able to adequately suppress their *H. pylori* levels to below detectable while on bismuth, but then commonly tested positive again after stopping bismuth [7]. This observation provides further evidence to suggest that bismuth, while bactericidal to some extent, is mainly providing suppressive effects. Importantly, while *H. pylori* is being suppressed to low levels, patients may experience improvement in their dyspepsia, gastritis, or ulcer-related symptomatology. There are several advantages to bismuth therapy for treatment of *H. pylori* despite its suppressive rather than curative effects; namely, it is available over the counter, is relatively inexpensive compared with prescription antibiotics, and is overall well tolerated. Being that bismuth is not an antibiotic and given its relatively benign side effect profile (black colored stools, black coated tongue, constipation, mild abdominal discomfort), it is safe to prescribe bismuth for an extended period.

Here, we report an interesting case of a treatment-resistant *H. pylori* infection in a 67-year-old female that was ultimately symptomatically controlled, rather than eradicated, with bismuth subsalicylate monotherapy. In our opinion, this is a reasonable and simple option given the significant financial, emotional, and potentially carcinogenic burden that persistent disease has on patients like the one presented. This case presents learning opportunities involving important perspectives on the growing antibiotic resistance of *H. pylori*, the efficacy of nonantibiotic treatment options for such an infection, and the importance of patient–physician collaboration when faced with difficult cases.

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Patient consent. Several attempts to reach the patient to obtain written consent were unsuccessful. The design of the work conforms to the standards of the local ethical committee.

Author contributions. All authors contributed to the writing of the manuscript and had access to the data presented.

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