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# Impact of antimicrobial resistance rates on eradication of *Helicobacter pylori* in a United States population

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**Keywords**

metronidazole; clarithromycin; levofloxacin; amoxicillin; rifabutin; tetracycline; next generation sequencing; 23S rRNA

## INTRODUCTION

Rates of antimicrobial resistance to commonly used antimicrobials in the treatment of *Helicobacter pylori* infection are rapidly rising worldwide, resulting in an increase in eradication failures.[1] Surprisingly little is known of resistance within the United States, or its impact on treatment success, a major limitation to current national treatment recommendations.[2] Using next-generation sequencing methods, a rapid and efficient method to determine antimicrobial resistance profiles, resistance rates and their impact on eradication success were analyzed from the state of Rhode Island.

## METHODS

From January 2018 through August 2019, we reviewed pathology records of gastric biopsies from the Rhode Island (750 beds) and Miriam (250 beds) hospitals, Providence, Rhode Island. Only the first treatment of *H. pylori* infection per patient, during the study period, was included. Patient characteristics, eradication test results and *H. pylori* treatment regimens were extracted from electronic medical records. Antimicrobial resistance profiles were performed using the PyloriAR assay (American Molecular Laboratories, Vernon Hills,

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IL) which evaluates DNA mutations or variances in the *H. pylori* genome associated with resistance to fluoroquinolones, metronidazole, clarithromycin, ampicillin, tetracycline, and rifabutin using next-generation sequencing. From the formalin-fixed paraffin-embedded gastric biopsies collected for diagnostic histopathology, five 10 μm sections were digested with lysis buffer and proteinase K, and whole DNA extracted with Qiagen spin columns and QIACube devices. A real-time PCR was performed to quantitatively determine *H. pylori* presence by targeting *23S rRNA.* For samples with sufficient *H. pylori* DNA, targeted genes from the *H. pylori* genome were amplified, enriched, and then paired-end sequencing libraries were sequenced with the Illumina MiSeq platform (Illumina, Inc., San Diego, CA). The generated reads were mapped to the reference of *H. pylori* 26695 genome sequence to analyze DNA mutations or variances responsible for the resistance to corresponding antimicrobials.

## RESULTS

We identified 315 patients with a positive gastric biopsy for *H. pylori.* Among these, eradication test results were available for 199 (63.2%) patients (urea breath test [50.8%], stool antigen [39.7%], biopsy [9.5%]). Ten (5.0%) gastric biopsies had insufficient *H. pylori* DNA. Thus, a total of 189 patients were included in the antimicrobial resistance analyses. Their mean age was 45.2 years (range 3–92) and 129 (68.3%) were male. Race/ethnicity was as follows (%): Caucasian 55 (29.1), Black 45 (23.8), Asian 4 (2.1), unknown 2 (1.1), Hispanic/Latino 83 (43.9).

Treatment data with eradication test results were available for 187 (98.9%) patients, who were treated through the two study hospitals' providers. Treatment duration was for 14 days among 171 (91.4%) patients. A total of 101 (54.0%) patients received bismuth quadruple therapy, of which 89 (88.1%) had eradication success. A total of 86 (46.0%) patients received triple therapy of which 52 (60.5%) had eradication success. Quadruple therapy had a statistically significant higher eradication success compared to triple therapy (odds ratio [OR] 4.8, confidence interval [CI] 2.3–10.2, P<0.001).

Antimicrobial resistance rates, treatment regimens and eradication test results are shown in the Table. Resistance profiles by type of treatment regimen are provided in the Supplementary Table.

Among the 84 patients who received clarithromycin-containing regimens, strains with clarithromycin resistance were statistically significantly higher among eradication failures (19/34 [55.9%]) compared to eradication successes (7/50 [14%], P<0.001). Among the 123 patients who received metronidazole-containing regimens, the number of strains with metronidazole resistance was not statistically different between patients with eradication failures (7/19 [36.8%]) and eradication successes (34/104 [32.6%], P=0.72). Among the 34 metronidazole-containing regimens with eradication success and metronidazole resistant strains, 29 (85.3%) regimens were quadruple, 33 (97.1%) regimens included ≥1 other antimicrobials to which the strain was susceptible, and duration of therapy was 14 days for 32 (94.1%) regimens.

## DISCUSSION

In this 18-month study, we report recent antimicrobial resistance data among *H. pylori* strains and provide novel information on the efficacy of next-generation sequencing methods in determining resistance profiles. A total of 65.6% of *H. pylori* strains were resistant to one or more commonly used antimicrobials. Resistance to metronidazole, clarithromycin and levofloxacin ranged from 29.6–33.3%, similar to other U.S. studies.[3–5] Of note, a concerning 9.7% of strains in our study were resistant to all three antimicrobials.

Eradication success was documented for 75.4% of *H. pylori* infections and was significantly higher for quadruple versus triple therapy. Clarithromycin resistance correlated with treatment failure. The presence of metronidazole resistance, however, was not associated with a greater likelihood of treatment failures, consistent with other studies.[1,5] This finding suggests that that there may be little benefit to using metronidazole in the treatment of *H. pylori* infections or the measurement of metronidazole resistance is not clinically relevant. In this study, the great majority of treatment regimens for metronidazole-resistant *H. pylori* infections that were successful included at least one other antimicrobial to which the strain was susceptible, further questioning the benefit of adding metronidazole in eradication regimens.

Prior U.S. studies have used conventional microbiological antimicrobial susceptibility methods,[3–5] which are time consuming given the fastidious properties of *H.* pylori, and not always successful in clinical practice.[6] In this study, next-generation sequencing was performed and was successful for 95% of cases, with results available within 72 hours. This suggests that this method is both effective and rapid for clinical practice and can optimize *H. pylori* treatment regimens.

Limitations of this study include 1] generalizability to other U.S. areas 2] antimicrobial exposure prior to the collection of the *H.pylori* biopsy was not available. Thus, the impact of exposure to antimicrobial regimens for the prior treatment of *H.pylori* or other infections and resistance rates was not assessed, 3] differences in medication compliance and antimicrobial doses may have affected eradication success rates and 4] levofloxacin was not used in regimens, therefore correlation between resistance to this antimicrobial and eradication outcomes was not evaluated.

Our results emphasize the need to consider antimicrobial resistance when evaluating treatment regimens for *H. pylori* infections, especially in triple therapies. The low rates of amoxicillin, tetracycline and rifabutin resistance in this study suggest that regimens relying on these drugs are advisable. Lastly, this study provides initial data to support the use of next-generation sequencing as an efficient method for antimicrobial susceptibility testing for *H. pylori*.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## REFERENCES

1. Savoldi A et al. Prevalence of antibiotic resistance in *Helicobacter pylori*: a systematic review and meta-analysis in World Health Organization regions. Gastroenterology. 2018;155:1372.e17–1382.e17. [PubMed: 29990487]
2. Chey WD et al. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017;112:212–239. [PubMed: 28071659]
3. Shiota S et al. Antibiotic resistance of *Helicobacter pylori* among male United States veterans. Clin Gastroenterol Hepatol. 2015;13:1616–1624. [PubMed: 25681693]
4. Park JY et al. *Helicobacter pylori* Clarithromycin resistance and treatment failure are common in the USA. Dig Dis Sci. 2016;61:2373–2380. [PubMed: 26923948]
5. Graham DY et al. Rifabutin-Based Triple Therapy (RHB-105) for Helicobacter pylori Eradication: A Double-Blind, Randomized, Controlled Trial. Ann Int Med 2020; 172:795–802. [PubMed: 32365359]
6. Cover TL et al. (2018). *Helicobacter pylori* and other gastric *Helicobacter* species. *In*: Bennett JE, Dolin R, Blaser MJ (eds) Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (pp 2494–2502), Philadelphia, PA. Elsevier Saunders.

**Table.**

Antimicrobial resistance, treatment regimens and eradication success percentages

| **Antimicrobial (189 isolates)** | **Resistance(%)** |
|---|---|
| Resistance to ≥ 1 antimicrobials | 65.6 |
| Metronidazole | 33.3 |
| Clarithromycin | 30.0 |
| Levofloxacin | 29.6 |
| Amoxicillin | 1.1 |
| Rifabutin | 0.5 |
| Tetracycline | 0.5 |
| **Co-resistance patterns (124 isolates resistant to ≥ 1 antimicrobials)** | |
| Clarithromycin-Metronidazole-Levofloxacin | 9.7 |
| Metronidazole-Levofloxacin | 8.1 |
| Clarithromycin - Metronidazole | 7.3 |
| Clarithromycin -Levofloxacin | 7.3 |
| Clarithromycin- Levofloxacin-Tetracycline | 0.8 |
| Metronidazole-Levofloxacin-Amoxicillin | 0.8 |
| **Treatment regimen* (Total [%])** | **Eradication Success (%)** |
| All treatment regimens (187 [100]) | 75.4 |
| Quadruple regimens | |
| PPI-Tetracycline-Metronidazole-Bismuth (79 [42.2]) | 89.9 |
| PPI-Doxycycline-Metronidazole-Bismuth (18 [14.1]) | 83.3 |
| PPI-Clarithromycin- Amoxicillin-Metronidazole (4 [3.1]) | 75.0 |
| Triple regimens | |
| PPI-Clarithromycin- Amoxicillin (62 [48.4]) | 58.1 |
| PPI-Clarithromycin- Metronidazole (18 [14.1]) | 61.1 |
| PPI-Amoxicillin-Metronidazole (4 [3.1]) | 100 |
| PPI-Rifabutin-Amoxicillin (2 [1.6]) | 50.0 |

* 187 isolates with data on treatment regimen and eradication test

PPI: proton pump inhibitor