Open

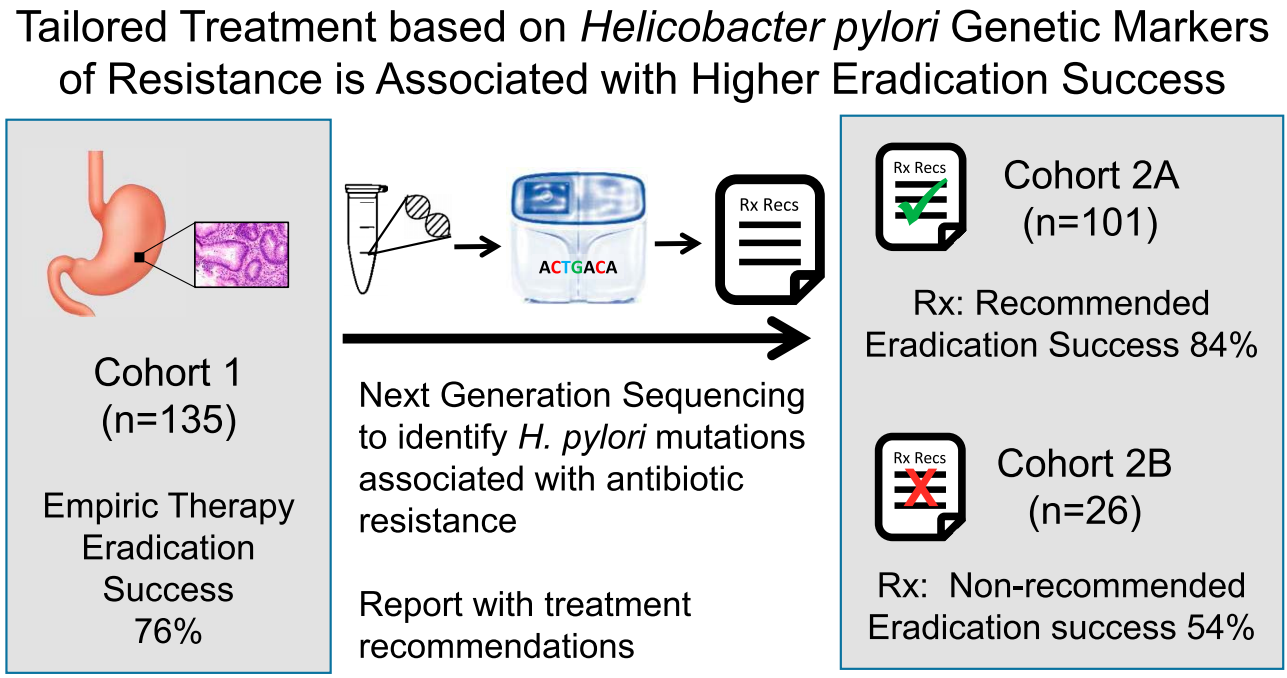
Tailored Treatment Based on *Helicobacter pylori* Genetic Markers of Resistance Is Associated With Higher Eradication Success

Linda C. Cummings, MD, MS[1,2,*], Leila S. Hojat, MD, MS[2,3,*], David C. Nguyen, MD[2,4], Lisa M. Stempak, MD[5,6], Daniel D. Rhoads, MD[7] and Navid Sadri, MD, PhD[5,6]

INTRODUCTION: **Increasing antimicrobial resistance with *Helicobacter pylori* infection has focused efforts to tailor eradication therapy based on identifying genetic markers of resistance to predict antimicrobial susceptibility.**

METHODS: **In this retrospective study, we report the effect of routine inclusion of antimicrobial susceptibility testing and recommendations for eradication therapy with gastric specimens with *H. pylori*.**

RESULTS: **The use of a recommended treatment regimen based on genetic markers of resistance was associated with an 84% rate of eradication success and 4.4 greater odds of eradication relative to unrecommended treatment.**



Cummings and Hojat et al. *Am J Gastroenterol. 2023*. doi: 10.14309/ajg.0000000000002085
Stomach image courtesy of Abigail Clark, University Hospitals Digestive Health Institute Medical Illustrator intern.

[1]Division of Gastroenterology and Liver Disease, Department of Medicine, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA; [2]Department of Medicine, School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA; [3]Division of Infectious Diseases & HIV Medicine, Department of Medicine, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA; [4]Medicine Service, Veterans Affairs Northeast Ohio Healthcare System, Cleveland, Ohio, USA; [5]Department of Pathology, School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA; [6]Department of Pathology, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA; [7]Department of Pathology, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, Ohio, USA.
Correspondence: Linda C. Cummings, MD, MS. E-mail: linda.cummings@case.edu.
*Linda C. Cummings and Leila S. Hojat contributed equally to this work.
Received June 15, 2022; accepted November 2, 2022; published online October 11, 2022

DISCUSSION: **This is the first study describing the use of *H. pylori* genetic resistance testing as standard of care.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C785 and http://links.lww.com/AJG/C786

Am J Gastroenterol 2023;118:360–363. https://doi.org/10.14309/ajg.0000000000002085

Helicobacter pylori infection is a leading cause of peptic ulcer disease and gastric cancer worldwide. Owing to widespread use of antibiotics, antimicrobial resistance is increasingly common in *H. pylori* infections. Molecular methods identifying *H. pylori* mutations associated with antibiotic resistance provide an efficient means to tailor eradication therapy at the onset of treatment. We previously reported the use of a culture-free next-generation sequencing (NGS) assay to analyze *H. pylori* extracted from formalin-fixed, paraffin-embedded gastric biopsy specimens for mutations conferring resistance to clarithromycin, levofloxacin, and tetracycline (1). In this study, we described the effect of using this NGS test to identify mutations associated with antimicrobial resistance (MAAR) as part of standard of care. Recommendations for eradication therapy based on MAAR findings were reported as an addendum to the gastric biopsy pathology report in the patient's medical record.

Table 1. Baseline characteristics and eradication success by initial treatment regimen before and after implementation of reflex reporting of *Helicobacter pylori* mutations associated with antimicrobial resistance with treatment recommendations

	Preintervention Cohort 1	Postintervention Cohort 2A[b]	Postintervention Cohort 2B[c]	*P* values[a]
Age, yr (mean ± SD)	57.6 ± 16.1	59.3 ± 16.2	61.1 ± 14.3	0.57
Female sex (%)	93 (68.9)	71 (70.3)	16 (61.5)	0.39
Race				0.99
White, n (%)	75 (55.6)	41 (40.6)	11 (42.3)	
Black (%)	52 (38.5)	52 (51.5)	13 (50.0)	
Other (%)	8 (5.9)	8 (7.9)	2 (7.7)	
Any antibiotic allergy (%)	34 (25.2)	25 (24.8)	10 (38.5)	0.16

	Preintervention		Postintervention			
			Cohort 2Ab[b]		Cohort 2B[c]	
	Treated	ES (%)	Treated	ES (%)	Treated	ES (%)
Quadruple therapy						
PPI-tetracycline-metronidazole-bismuth	21	18 (85.7)	35	31 (88.6)	1	1 (100)
PPI-amoxicillin-metronidazole-bismuth	4	4 (100)			6	4 (66.7)
Any quadruple therapy	25	22 (88.0)	35	31 (88.6)	7	5 (71.4)
Triple therapy						
PPI-clarithromycin-amoxicillin	89	69 (77.5)	51	43 (84.3)	11	5 (45.5)
PPI-clarithromycin-metronidazole	14	6 (42.8)	8	6 (75.0)	4	0 (0)
PPI-levofloxacin-amoxicillin	1	1 (100)	6	4 (66.7)		
PPI-amoxicillin-metronidazole	4	2 (50.0)			1	1 (100)
Any triple therapy	108	78 (72.2)	65	53 (81.5)	16	6 (37.5)
Dual therapy						
PPI-levofloxacin					1	1 (100)
PPI-metronidazole					1	1 (100)
PPI-amoxicillin	1	1 (100)	1	1 (100)		
Any dual therapy	1	1 (100)	1	1 (100)	2	2 (100)
Other[d]	1	1 (100)			1	1 (100)
All regimens	135	102 (75.6)	101	85 (84.2)	26	14 (53.8)

ES, eradication success; PPI, proton pump inhibitor.
[a]Comparison of baseline characteristics between cohort 2A and cohort 2B.
[b]Cohort 2A was prescribed a treatment regimen consistent with report recommendations.
[c]Cohort 2B was prescribed a treatment regimen that was not consistent with report recommendations.
[d]Subject in cohort 1 was prescribed amoxicillin, rifabutin, and PPI; subject in cohort 2B was prescribed amoxicillin, doxycycline, metronidazole, and PPI.

Table 2. Predicted antimicrobial resistance after implementation of reflex reporting of *Helicobacter pylori* mutations associated with antimicrobial resistance

	All samples tested after intervention (n = 603)		Cohort 2 (n = 127)	
	No. of cases	% of total	No. of cases	% of total
Clarithromycin resistance[a]	195	32.3	43	33.9
Levofloxacin resistance[b]	236	39.1	46	36.2
Tetracycline resistance[c]	14	2.3	3	2.4
Clarithromycin + levofloxacin resistance	115	19.1	20	15.7
Clarithromycin + tetracycline resistance	8	1.3	1	0.8
Levofloxacin + tetracycline resistance	7	1.2	2	1.6
Clarithromycin + levofloxacin + tetracycline resistance	5	0.8	1	0.8
No resistance identified[a,b,c]	282	46.8	57	44.9

[a]23S rRNA gene mutations (A2142C/G and A2143G) predicted to confer resistance to clarithromycin.
[b]*gyrA* gene mutations (87N>H/I/K and 91D>G/H/M/N/Y) predicted to confer resistance to levofloxacin.
[c]16S rRNA gene mutations (A926C/G and A928G) predicted to confer resistance to tetracycline.

A multidisciplinary team including pathologists with expertise in genomic sequencing (N.S.) and microbiology (D.D.R.), infectious disease experts (L.S.H., D.C.N.), and a gastroenterologist (L.C.C.) convened in early 2020 to develop specific treatment recommendations based on susceptibility testing to guide clinicians in selection of eradication therapy for *H. pylori*. Treatment recommendations for 14-day eradication regimens were developed based on available guidelines from North America (2,3) and included recommendations to ascertain previous macrolide exposure and to consider allergy testing in patients reporting penicillin allergy. Beginning in June 2020, *H. pylori* MAAR testing for clarithromycin, levofloxacin, and tetracycline was included as a reflex test for all gastric specimens with *H. pylori* identified by histopathology within the University Hospitals Health System (including 12 hospitals) in northeast Ohio (see Supplementary Methods, Supplementary Digital Content 1, http://links.lww.com/AJG/C785). MAAR testing with treatment recommendations was reported as an addendum to the pathology report. Treatment recommendations (see Supplementary Table 1, Supplementary Digital Content 2, http://links.lww.com/AJG/C786) avoided the use of antibiotics expected to be resistant.

This study aimed to evaluate the effect of MAAR-informed treatment recommendations on eradication success. Institutional Review Board approval was obtained from University Hospitals Cleveland Medical Center. Information on the prescribed eradication therapy regimen was extracted from the medical record. Results of testing for confirmation of eradication (urea breath test, stool antigen test, or repeat biopsies) for patients receiving eradication therapy were tracked. We evaluated rates of eradication success before and after implementation of reflex MAAR testing in the period from February 1, 2019, to November 1, 2021, in patients without documentation of previous treatment for *H. pylori* and compared eradication rates using Pearson χ^2 tests. Patients with treatment data before the intervention were designated cohort 1. Among patients with MAAR results and treatment data after the intervention, we compared eradication success between patients prescribed a regimen consistent with the recommended therapy (designated cohort 2A) and those prescribed a regimen that deviated from the recommendations (designated cohort 2B).

Before the intervention, 866 subjects were considered. Of them, 16% (135/866; cohort 1) had no previous treatment, a documented eradication therapy regimen, and documented eradication testing results. The eradication success rate was 76% (102/135), with a higher eradication success for subjects receiving quadruple therapy (Table 1).

After the intervention, 603 subjects were considered. Of them, 21% (127/603; cohort 2) had no previous treatment, a documented eradication therapy regimen, and documented eradication testing results. MAAR for clarithromycin, levofloxacin, and combined levofloxacin/clarithromycin resistance were detected in 34% (43/127), 36% (46/127), and 16% (20/127) of subjects, respectively, after the intervention (Table 2). Eighty percent (101/127) of cohort 2 was prescribed a recommended regimen (cohort 2A), and 20% (26/127) of subjects were prescribed an unrecommended regimen (cohort 2B). Based on chart review, 58% (15/26) of subjects in cohort 2B were prescribed treatment before the release of the MAAR report. In an additional 31% (8/26) of subjects in cohort 2B for whom treatment was prescribed on or after the release of the MAAR report, provider notes regarding treatment did not acknowledge MAAR testing results.

After the intervention, the eradication success rate was 84% (85/101) for cohort 2A and 54% (14/26) for cohort 2B ($P = 0.001$). Among 70 subjects in cohort 2 with any antimicrobial resistance, the eradication success rate was 84% (41/49) for cohort 2A and 48% (10/21) for cohort 2B ($P = 0.002$). In a multivariable logistic regression including all subjects in cohort 2, being prescribed a recommended regimen (cohort 2A) was independently associated with 4.4 times greater odds of treatment success after

Table 3. Factors associated with eradication success after implementation of reflex reporting of *Helicobacter pylori* mutations associated with antimicrobial resistance

Covariate	Odds ratio	95% CI	*P* value
Cohort 2A vs cohort 2B[a]	4.43	1.61–12.51	0.004
Any mutation associated with antimicrobial resistance present	0.76	0.27–2.08	0.59
Age	1.02	0.98–1.05	0.37
Male sex	0.93	0.36–2.57	0.89
Race			
White	Reference		
Black	0.92	0.33–2.47	0.86
Other	0.21	0.04–1.01	0.05
Any antibiotic allergy present	0.60	0.22–1.71	0.33

CI, confidence interval.
[a]Cohort 2A was prescribed a treatment regimen consistent with report recommendations. Cohort 2B was prescribed a treatment regimen that was not consistent with report recommendations.

adjusting for any antimicrobial resistance, age, sex, race, and any antibiotic allergy (95% confidence interval 1.61–12.51; Table 3).

The cure rate with empiric therapy in our population (represented by cohort 1) was <90%, the threshold suggested in a recently proposed algorithm for the use of susceptibility testing before therapy (4). Notably, mutations associated with antibiotic resistance were identified in 55% of samples tested. Of most importance, we found that treatment with regimens containing an antimicrobial drug for which the *H. pylori* is expected to be resistant based on testing (cohort 2B) was more likely to fail than when using a recommended regimen (cohort 2A).

Recent communications have reported the use of NGS methods to evaluate *H. pylori* antimicrobial resistance (5–7). One study reported a 53% rate of clarithromycin resistance (6). Our study revealed a 34% rate of clarithromycin resistance, which well exceeds the 10%–18% rate reported in a systematic review for Americas region (8) and the 15% threshold above which guidelines recommend against empiric clarithromycin triple therapy (2). To our knowledge, this is the first study describing the use of *H. pylori* genetic resistance testing as standard of care. The study demonstrates that routine evaluation of MAAR for *H. pylori* can direct initial therapy, improve patient outcomes, and promote antimicrobial stewardship by avoiding the use of ineffective antibiotics. Moreover, this analysis reports local eradication success rates for specific regimens, in keeping with recommendations in recent literature on *H. pylori* therapy (9–11). Our study is limited by lack of eradication data on the majority of patients, inability to assess adherence to eradication therapy, and the inability to confirm that clinician treatment decisions were made in response to treatment guidance. Future studies should identify methods to improve adoption of recommended therapies and evaluate the utility of personalized treatment recommendations paired with active antimicrobial stewardship interventions targeting *H. pylori* eradication.

CONFLICTS OF INTEREST

Guarantor of the article: Navid Sadri, MD, PhD.

Specific author contributions: L.C.C.: conceptualization: equal, formal analysis: equal, writing-original draft: lead. L.S.H.: conceptualization: equal, formal analysis: equal, statistical analysis: lead, IRB: lead, writing-original draft: equal. D.C.N.: data curation: supporting, writing—review and editing: supporting. L.M.S.: writing—review and editing: equal. D.D.R.: conceptualization: equal, writing—review and editing: equal. N.S.: conceptualization: lead, methodology: lead, data curation: lead, formal analysis: equal, writing—review and editing: equal. All authors have approved the final draft.

Financial support: Funding for open access publication charges provided by University Hospitals Health System.

Potential competing interests: None to report.

REFERENCES

1. Nezami BG, Jani M, Alouani D, et al. *Helicobacter pylori* mutations detected by next-generation sequencing in formalin-fixed, paraffin-embedded gastric biopsy specimens are associated with treatment failure. J Clin Microbiol 2019;57(7):e01834–18.
2. Chey WD, Leontiadis GI, Howden CW, et al. ACG clinical guideline: Treatment of *Helicobacter pylori* infection. Am J Gastroenterol 2017;112(2):212–38.
3. Fallone CA, Chiba N, van Zanten SV, et al. The Toronto consensus for the treatment of *Helicobacter pylori* infection in adults. Gastroenterology 2016;151(1):51–69.
4. Graham DY, Moss SF. Antimicrobial susceptibility testing for *Helicobacter pylori* is now widely available: When, how, why. Am J Gastroenterol 2022;117(4):524–8.
5. Argueta EA, Alsamman MA, Moss SF, et al. Impact of antimicrobial resistance rates on eradication of *Helicobacter pylori* in a US population. Gastroenterology 2021;160(6):2181–3.
6. Moss SF, Dang LP, Chua D, et al. Comparable results of *Helicobacter pylori* antibiotic resistance testing of stools versus gastric biopsies using next generation sequencing. Gastroenterology 2022;162(7):2095–7.
7. Marrero Rolon R, Cunningham S, Mandrekar JN, et al. Clinical evaluation of a real-time PCR assay for simultaneous detection of *Helicobacter pylori* and genotypic markers of clarithromycin resistance directly from stool. J Clin Microbiol 2021;59(5):e03040–20.
8. Savoldi A, Carrara E, Graham DY, et al. Prevalence of antibiotic resistance in *Helicobacter pylori*: A systematic review and meta-analysis in World Health Organization regions. Gastroenterology 2018;155(5):1372–82.
9. Shah SC, Iyer PG, Moss SF. AGA clinical practice update on the management of refractory *Helicobacter pylori* infection: Expert review. Gastroenterology 2021;160(5):1831–41.
10. Graham DY, Liou JM. Primer for development of guidelines for *Helicobacter pylori* therapy using antimicrobial stewardship. Clin Gastroenterol Hepatol 2022;20(5):973–83.
11. Shiotani A, Roy P, Lu H, et al. *Helicobacter pylori* diagnosis and therapy in the era of antimicrobial stewardship. Therap Adv Gastroenterol 2021;14:17562848211064080.