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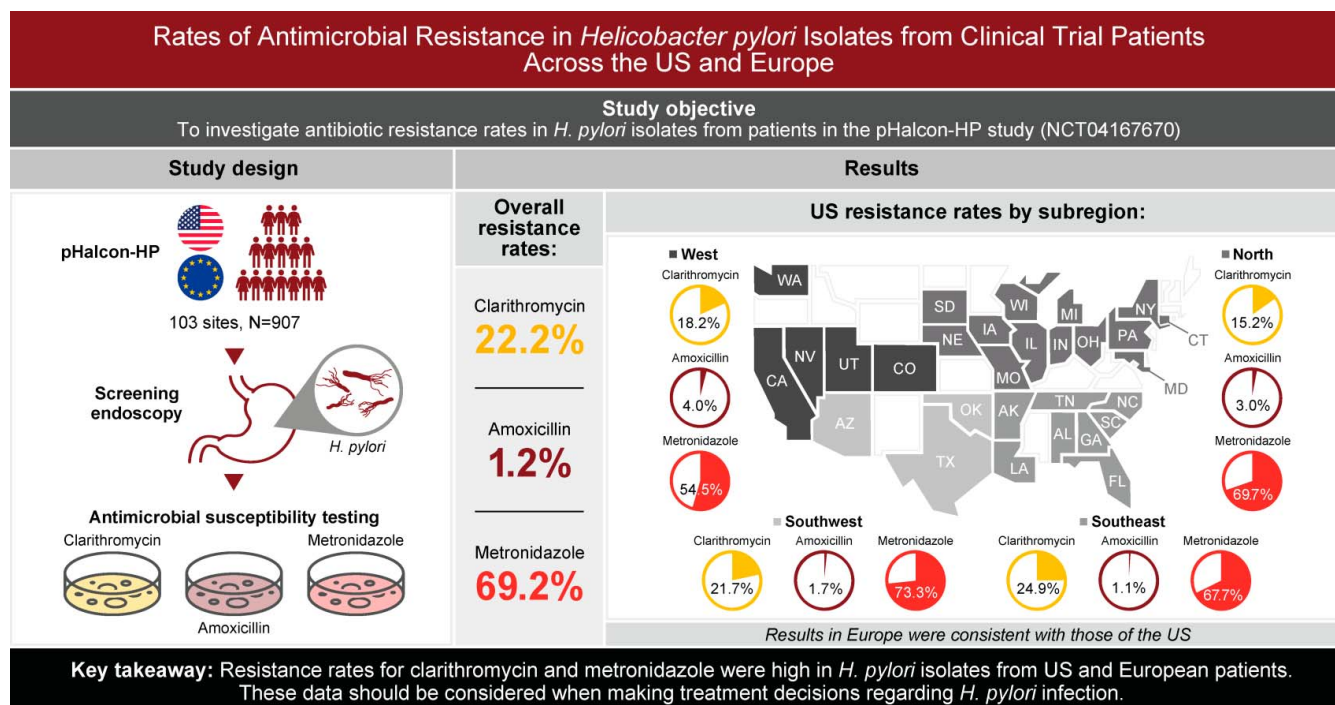
Rates of Antimicrobial Resistance in *Helicobacter pylori* Isolates From Clinical Trial Patients Across the US and Europe

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INTRODUCTION: Guidelines recommend that proton pump inhibitor-based triple regimens with clarithromycin not be used for *Helicobacter pylori* infection in areas where clarithromycin resistance is ≥15%, or in patients with prior macrolide use. Up-to-date information on local resistance patterns is limited, especially in the US. Here, we report resistance rates to antibiotics commonly used to treat *H. pylori* from a large study conducted in the US and Europe (pHalcon-HP).

METHODS: Gastric mucosal biopsies were collected from adult participants with *H. pylori* infection during screening. Minimum inhibitory concentrations were determined via agar dilution for clarithromycin, amoxicillin, and metronidazole, with breakpoints ≥1 μg/mL, >0.125 μg/mL, and >8 μg/mL, respectively. Resistance rates were obtained for the US and Europe, and also for US subregions and participating European countries.

Rates of Antimicrobial Resistance in *Helicobacter pylori* Isolates from Clinical Trial Patients Across the US and Europe

Study objective
To investigate antibiotic resistance rates in *H. pylori* isolates from patients in the pHalcon-HP study (NCT04167670)

Study design

pHalcon-HP

103 sites, N=907

Screening endoscopy

H. pylori

Antimicrobial susceptibility testing
Clarithromycin   Metronidazole   Amoxicillin

Overall resistance rates:

Clarithromycin
22.2%

Amoxicillin
1.2%

Metronidazole
69.2%

Results

US resistance rates by subregion:

West
Clarithromycin 18.2%
Amoxicillin 4.0%
Metronidazole 54.5%

North
Clarithromycin 15.2%
Amoxicillin 3.0%
Metronidazole 69.7%

Southwest
Clarithromycin 21.7%
Amoxicillin 1.7%
Metronidazole 73.3%

Southeast
Clarithromycin 24.9%
Amoxicillin 1.1%
Metronidazole 67.7%

Results in Europe were consistent with those of the US

Key takeaway: Resistance rates for clarithromycin and metronidazole were high in *H. pylori* isolates from US and European patients. These data should be considered when making treatment decisions regarding *H. pylori* infection.

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RESULTS: **Resistance rates were established in isolates from 907 participants. Overall, 22.2% were resistant to clarithromycin, 1.2% to amoxicillin, and 69.2% to metronidazole. Resistance in the US and Europe was similar; metronidazole resistance was the most prevalent (50%–79%) and amoxicillin the least (≤5%). In all subregions, ≥15% of isolates were resistant to clarithromycin, except the UK (0/8 isolates). Among clarithromycin-resistant isolates, 75% were also metronidazole-resistant. Two US isolates were resistant to clarithromycin and amoxicillin; one of these was also metronidazole-resistant.**

DISCUSSION: **The resistance rates observed in this study argue against the continued empiric use of proton pump inhibitor-based triple therapy containing clarithromycin, per treatment guidelines, and highlight the need for antibiotic resistance surveillance and novel treatment strategies for *H. pylori* infection in the US and Europe.**

INTRODUCTION

Helicobacter pylori currently infects over half of the world's population (1). Infection causes chronic gastritis and is the major risk factor for peptic ulcer disease, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma (1,2). Therapies that were developed in the 1990s include the combination of a proton pump inhibitor (PPI), clarithromycin and amoxicillin. Although these are still used globally, eradication rates have declined sharply during the last decade, due mainly to increased clarithromycin resistance (3–5).

Resistance rates to some of the antibiotics commonly used for the treatment of *H. pylori* infection are high; a global meta-analysis identified *H. pylori* primary and secondary resistance rates to clarithromycin, metronidazole and levofloxacin of more than 15% in nearly all regions (6). Furthermore, use of these antibiotics for other indications is widespread and increasing (7). In Europe, resistance of *H. pylori* to clarithromycin and levofloxacin has been linked to the widespread use of macrolides and fluoroquinolones, respectively (8,9). Consequently, recent guidelines have noted the effect of prior antibiotic exposure on susceptibility, and recommend that antibiotic history be taken into account in treatment decision-making (2,4).

In Europe, resistance rates to macrolides ranged from 4.8% to 36.9% in 2018 (8). In the US, contemporary data are limited (10), with most studies confined to small geographic regions or limited in the number of subjects evaluated (11–14). In a recent US clinical trial, antimicrobial susceptibility testing (AST) data from 345 patients showed 43.6% metronidazole resistance across the US, and 23.2% clarithromycin resistance in the Eastern US. (15). Both the Maastricht V/Florence and American College of Gastroenterology treatment guidelines recommend that the choice of regimen should be based upon knowledge of local resistance patterns (2,4). However, this information is particularly scarce in the US. (2,4). Furthermore, individual AST is currently not widely performed in the US. (4). Given the potentially serious consequences of failure to cure *H. pylori* infection, improved understanding of current, local resistance patterns is crucial for making treatment choices, thereby avoiding the use of unnecessary antibiotics in line with the strong recommendation of the World Health Organization, and increasing the chances of successful eradication (6,16).

A recent large clinical trial evaluated vonoprazan, a potassium-competitive acid blocker, with clarithromycin and amoxicillin as triple therapy, or with amoxicillin as dual therapy, for the treatment of *H. pylori* infection (pHalcon-HP; NCT04167670). In that trial, isolates were obtained from patients from multiple centers across the US and Europe for AST. Here, we report antimicrobial susceptibility data from 907 participants in 103 centers across the US and 5 European countries. This represents the largest collection of antimicrobial susceptibility data that includes participants from the US.

METHODS

Ethical practices

pHalcon-HP; NCT04167670 was conducted in compliance with the principles of the Declaration of Helsinki and in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice. Institutional review boards at each participating institution approved the trial protocol, and all participants provided written informed consent.

Participants and biopsy sampling

Participants had *H. pylori* infection confirmed by ^{13}C-urea breath test and gastric biopsy specimens. Full eligibility criteria can be found in the clinical data publication (17). Gastric mucosal biopsy samples were taken at the screening endoscopy: one sample from the greater curve of the antrum and one from the lesser curve of the gastric body. The specimens were immediately introduced into Brucella broth with 20% glycerol and frozen at −20 °C or −70 °C, depending on freezer availability at the different sites, prior to transport to the central laboratory (Microbiology Specialists, Houston, TX). Upon receipt, specimens were ground, and 100 μg/mL of homogenized tissue was placed on blood agar, as well as on *H. pylori* medium including vancomycin, trimethoprim, cefsulodin, and amphotericin B (Anaerobe Systems, Morgan Hill, CA). Plates were placed in an Anoxomat jar (Advanced Instruments, Norwood, MA) for incubation at 35 ± 1 °C for up to 14 days. A microaerobic gas mixture (80% nitrogen, 10% carbon dioxide, 5% hydrogen and 5% oxygen) was used and an *H. pylori*-positive control was added to each jar. The remaining 300 μg/mL of specimen were then frozen at −70 °C.

H. pylori isolation and identification

After 72 hours, jars were opened and checked for growth. If not positive, they were re-incubated and re-observed at 7 and 14 days. If positive for small, gray and translucent colonies, they were Gram-stained, with a selection for small Gram-negative curved

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Table 1. Baseline characteristics and demographics of patients with resistant and susceptible *Helicobacter pylori* isolates

	Clarithromycin-resistant (n = 201)	Clarithromycin-susceptible[a] (n = 706)	Amoxicillin-resistant (n = 11)	Amoxicillin-susceptible (n = 896)	Metronidazole-resistant (n = 628)	Metronidazole-susceptible (n = 279)
Age, yr, mean (SD)	51.5 (13.6)	50.9 (13.6)	54.8 (11.7)	51.0 (13.6)	50.6 (13.8)	51.9 (13.2)
Sex, n (%) female	140 (69.7)	427 (60.5)[b]	9 (81.8)	558 (62.3)	402 (64.0)	165 (59.1)
Race, n (%)						
Non-white	13 (6.5)	81 (11.5)[b]	2 (18.2)	92 (10.3)	60 (9.6)	34 (12.2)
American Indian or Alaska Native	1 (0.5)	1 (0.1)	0	2 (0.2)	1 (0.2)	1 (0.4)
Asian	2 (1.0)	12 (1.7)	1 (9.1)	13 (1.5)	5 (0.8)	9 (3.2)
Black or African American	10 (5.0)	60 (8.5)	0	70 (7.8)	50 (8.0)	20 (7.2)
Native Hawaiian or other Pacific Islander	0	1 (0.1)	0	1 (0.1)	1 (0.2)	0
Other	0	7 (1.0)	1 (9.1)	6 (0.7)	3 (0.5)	4 (1.4)
Unknown	1 (0.5)	5 (0.7)	0	6 (0.7)	3 (0.5)	3 (1.1)
White	187 (93.0)	620 (87.8)[b]	9 (81.8)	798 (89.1)	565 (90.0)	242 (86.7)
Ethnicity, n (%)						
Hispanic or Latino	63 (31.3)	181 (25.6)	6 (54.5)	238 (26.6)	164 (26.1)	80 (28.7)
Not Hispanic or Latino, or unknown	138 (68.7)	525 (74.4)	5 (45.5)	658 (73.4)	464 (73.9)	199 (71.3)
Height, cm, mean (SD)	166.7 (9.7)	167.5 (9.8)	162.4 (8.3)	167.4 (9.8)	167.2 (9.6)	167.7 (10.2)
Weight, kg, mean (SD)	82.2 (16.8)	83.0 (19.3)	69.4 (12.2)	83.0 (18.8)	82.2 (18.6)	84.2 (19.3)
BMI, mean (SD)	29.6 (5.7)	29.5 (6.0)	26.4 (4.7)	29.5 (5.9)	29.3 (5.8)	29.9 (6.3)
Smoking status, n (%)						
Current smoker	41 (20.4)	166 (23.5)	1 (9.1)	206 (23.0)	152 (24.2)	55 (19.7)
Ex-smoker	36 (17.9)	148 (21.0)	0	184 (20.5)	132 (21.0)	52 (18.6)
Never smoked	124 (61.7)	392 (55.5)	10 (90.9)	506 (56.5)	344 (54.8)	172 (61.6)
Alcohol use, n (%)						
Couple of d per mo	66 (32.8)	240 (34.0)	4 (36.4)	302 (33.7)	209 (33.3)	97 (34.8)
Couple of d per wk	34 (16.9)	135 (19.1)	2 (18.2)	167 (18.6)	122 (19.4)	47 (16.8)
Everyday	3 (1.5)	14 (2.0)	1 (9.1)	16 (1.8)	16 (2.5)	1 (0.4)
Never	98 (48.8)	317 (44.9)	4 (36.4)	411 (45.9)	281 (44.7)	134 (48.0)

BMI, body mass index.

[a]Please note that clarithromycin susceptibility status was classed into 3 categories: susceptible; intermediate; and resistant. For the purpose of this analysis, "clarithromycin susceptible" refers to patients with isolates classed as susceptible or intermediate.

[b]Denotes $P < 0.05$ for comparison between the proportion of patients in reported demographic with resistant vs susceptible isolates. Comparisons between patients with resistant and susceptible isolates were performed using t test for continuous variables and χ^2 test for categorical variables. Statistical comparisons were not performed for amoxicillin resistant and susceptible isolates due to the small number of resistant isolates.

rods. Selected colonies were analyzed using oxidase, catalase, and urease tests. If the colonies were positive for all 3 tests, with the urease test providing a positive test within minutes, 3 plates were prepared for AST.

Antimicrobial susceptibility testing

The minimum inhibitory concentrations of amoxicillin, clarithromycin and metronidazole against each isolate were determined using the agar dilution method. Each antimicrobial was prepared at a concentration of 0.03–128 mg/L. Plates were inoculated using a Steers replicator and incubated in the Anoxomat microaerobic system for 48–72 hours. The resistance breakpoints were defined as: clarithromycin ≥1 µg/mL, amoxicillin >0.125 µg/mL and metronidazole >8 µg/mL, based on the Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing criteria (18,19).

Statistical analysis

Among participants with AST results available, resistance rates to each antibiotic were summarized overall, by region (US and Europe), and by US subregion or European country. Numbers of participants with isolates resistant to more than one antibiotic were also tabulated. Baseline characteristics were summarized for participants with isolates susceptible or resistant to each antibiotic. Statistical analyses were performed using SAS for Windows, version 9.4 (SAS Institute).

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RESULTS

Overview of participants with resistant and susceptible isolates

Overall, samples from 907 participants underwent AST (see Supplementary Figure 1, http://links.lww.com/AJG/C723). Clarithromycin resistance was detected in isolates from 201 participants (22.2%) (Table 1). Only 11 participants (1.2%) had isolates that were amoxicillin-resistant, but 628 (69.2%) harbored ones that were metronidazole-resistant. Baseline characteristics, including age and body mass index, were generally equally distributed between participants with isolates resistant and susceptible to the antibiotics, except for sex and white/non-white race which were unevenly distributed among those with clarithromycin-resistant and susceptible isolates (Table 1). A greater proportion of patients with clarithromycin-resistant isolates compared with susceptible isolates were female (69.7% vs 60.5%, $P < 0.05$) and white (93.0% vs 87.8%, $P < 0.05$). Due to the small number of patients with amoxicillin-resistant isolates, statistical comparisons of baseline characteristics based on amoxicillin susceptibility status were not performed. Additional demographic data stratified by antibiotic resistance or susceptibility are given in Table 1.

Resistance data by geographical location

Overall, resistance rates between the US and Europe were broadly comparable (Table 2). Clarithromycin resistance was above 15% in all US subregions and in all European countries, except the UK, where none of the 8 isolates tested were clarithromycin-resistant. Among US regions, the greatest prevalence of clarithromycin resistance was in the Southeast (24.9%; 47/189) (Figure 1); among the European countries, it was in the Czech Republic (26.7%; 4/15). Two US regions (Southwest and Southeast) and 2 European countries (Czech Republic and Poland) had clarithromycin-resistant isolates in over 20% of participants.

In the US, resistance to metronidazole ranged from 54.5% (54/99) in the West to 73.3% (44/60) in the Southwest (Figure 1) and, in Europe, from 50.0% (4/8) in the UK to 79.4% (85/107) in Bulgaria.

Of the 11 participants with amoxicillin-resistant isolates, 8 (72.7%) were from the US, and half of those were in the West.

Clinical conditions

Participants with resistant and susceptible isolates had similar proportions of underlying conditions and indications for treatment of H. pylori infection at study entry (Table 3). Nearly all participants had dyspepsia, regardless of the presence or absence of resistance.

Prevalence of multi-resistance

A total of 7 of the 11 (63.6%) participants with amoxicillin-resistant isolates also had isolates resistant to at least one other antibiotic. This included one participant in the US with an isolate resistant to all 3 antibiotics, and one other US participant with resistance to both clarithromycin and amoxicillin. Five additional participants had isolates resistant to both metronidazole and amoxicillin: 3 from the US, one from Hungary and one from Poland. In most participants with clarithromycin-resistant isolates, there was also resistance to metronidazole (75.1%; 151/201). Of these 151 participants, 90 were from Europe (59.6%) and 61 were from the US (40.4%).

DISCUSSION

These data, from the largest registered clinical trial in participants with H. pylori infection to take place in the US and Europe, provide important and current insight into the prevalence of resistant H. pylori isolates. The results confirm that resistance to clarithromycin and metronidazole is high in these regions. All US subregions and European countries had clarithromycin resistance rates >15%, except the UK where the sample size was too small to provide a reliable estimate. Furthermore, most of these clarithromycin-resistant isolates were also metronidazole-resistant. Given the impact of clarithromycin resistance on treatment effectiveness, Maastricht V and American College of Gastroenterology clinical practice guidelines both recommend that triple regimens with a PPI and clarithromycin should not be used empirically where local resistance rates are greater than 15%, is unknown, or if the patient has had prior exposure to a macrolide (2,4). Triple regimens containing a PPI and clarithromycin are still commonly prescribed in the US and Europe

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Table 2. Resistance rates in the US and Europe in pHalcon-HP

n (%)	Clarithromycin	Amoxicillin	Metronidazole
US (n = 381)	83 (21.8)	8 (2.1)	249 (65.4)
US-West (n = 99)	18 (18.2)	4 (4.0)	54 (54.5)
US-Southwest (n = 60)	13 (21.7)	1 (1.7)	44 (73.3)
US-Southeast (n = 189)	47 (24.9)	2 (1.1)	128 (67.7)
US-North (n = 33)	5 (15.2)	1 (3.0)	23 (69.7)
Europe (n = 526)	118 (22.4)	3 (0.6)	379 (72.1)
Bulgaria (n = 107)	21 (19.6)	0	85 (79.4)
Czech Republic (n = 15)	4 (26.7)	0	11 (73.3)
Hungary (n = 20)	3 (15.0)	1 (5.0)	14 (70.0)
Poland (n = 376)	90 (23.9)	2 (0.5)	265 (70.5)
UK (n = 8)	0	0	4 (50.0)

US-West: California, Colorado, Nevada, Utah, and Washington. US-Southwest: Arizona, Oklahoma, and Texas. US-Southeast: Alabama, Arkansas, Florida, Georgia, Louisiana, North Carolina, South Carolina, Tennessee, and Virginia. US-North: Connecticut, Illinois, Indiana, Iowa, Maryland, Michigan, Missouri, Nebraska, New York, Ohio, Pennsylvania, South Dakota, and Wisconsin.
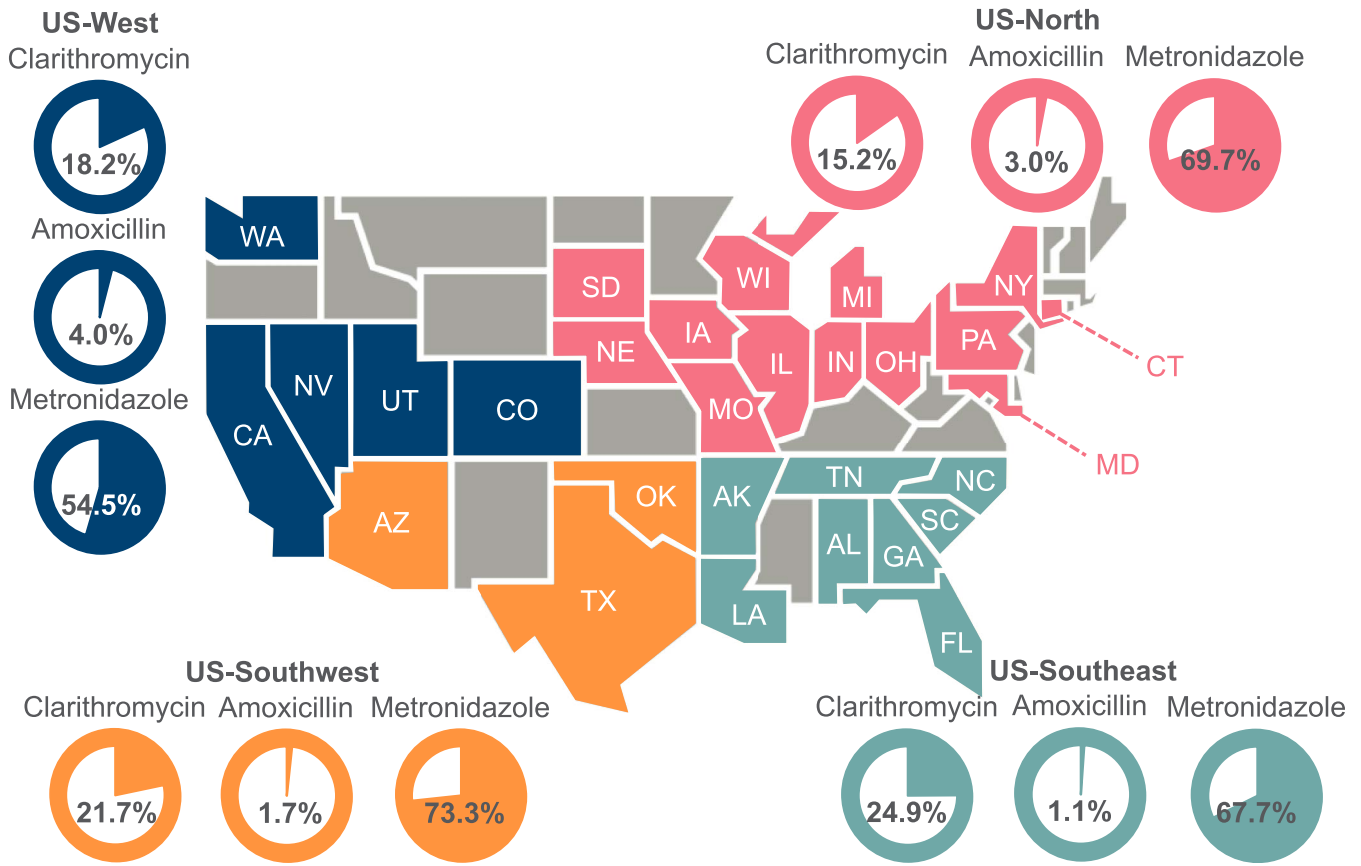
Figure 1. Clarithromycin, amoxicillin and metronidazole resistance rates in the US. Gray color-coding indicates states that did not contain centers that participated in the pHalcon-HP study. Participating states are color-coded according to their assigned US-subregion.

(3,20), although, currently, AST is usually not performed (3,4). These data indicate that the current empiric management of patients with *H. pylori* infection is inadequate and results in a large proportion in whom treatment fails, leaving persistently infected patients at risk of potentially serious complications.

The high prevalence of resistance, including dual resistance, emphasizes the need to optimize the management of *H. pylori* infection by improving antimicrobial stewardship and treatment options. A study of 135 male veterans with *H. pylori* infection in Houston, Texas, in 2015 showed resistance rates of 16.4% to

clarithromycin and 20.3% to metronidazole (14). In the current study, the US subregion that included Texas had a prevalence of clarithromycin resistance of 21.7% and metronidazole resistance of 73.3%, indicating a rise within the last 5 years. Resistance to metronidazole, which is commonly used for parasitic and other infections, has been associated with its prior use. Furthermore, the use of nitroimidazoles including metronidazole for gynecological and dental infections may further promote resistance (5,21,22). Although *in vitro* metronidazole resistance rates can vary widely between studies due to different microbiology

Table 3. Clinical conditions by *Helicobacter pylori* resistance status

n (%)	Clarithromycin-resistant (n = 201)	Clarithromycin-susceptible (n = 706)	Amoxicillin-resistant (n = 11)	Amoxicillin-susceptible (n = 896)	Metronidazole-resistant (n = 628)	Metronidazole-susceptible (n = 279)
Dyspepsia[a]	196 (97.5)	692 (98.0)	11 (100)	877 (97.9)	617 (98.2)	271 (97.1)
Recent/new diagnosis of non-bleeding peptic ulcer	3 (1.5)	18 (2.5)	0	21 (2.3)	15 (2.4)	6 (2.2)
History of peptic ulcer not previously treated for *H. pylori*	4 (2.0)	18 (2.5)	0	22 (2.5)	17 (2.7)	5 (1.8)
Long-term NSAID at a stable dose	6 (3.0)	19 (2.7)	0	25 (2.8)	20 (3.2)	5 (1.8)

NSAID, non-steroidal anti-inflammatory drug.

[a]Includes patients reporting ≥2 weeks of dyspepsia and/or a confirmed diagnosis of functional dyspepsia. The American College of Gastroenterology 2017 guidelines (4) recommend testing patients with diagnosed functional dyspepsia for *H. pylori* infection.

techniques and difficulties with assay reproducibility, they may also indicate a trend (22). While metronidazole resistance may negatively influence eradication rates, it is not associated with treatment failure to the same extent as clarithromycin resistance (2,4). Thus, the consequences of the high rates of metronidazole resistance remain to be determined. Optimizing the management of *H. pylori* infection could help to address further rises in resistance rates, including multi-drug resistance, by avoiding the use of unnecessary antibiotics and thereby reducing the risk of resistance acquisition (8,16). Changes to current management could include improving antibiotic stewardship, and optimization of current therapeutic regimens, to improve eradication rates without necessitating the use of additional antibiotics. In part, this could be achieved through the more frequent use of AST to optimize treatment regimens, given the availability of real-time polymerase chain reaction kits to detect *H. pylori* and its resistance to clarithromycin at low cost, and the familiarity with this process in laboratories following the COVID-19 pandemic. Tailoring therapies based on known resistance has been shown to improve eradication rates and increase cost efficiency over empiric therapy when used in areas with high local resistance rates, such as the rates reported in this current study (23–25). However, AST is currently infrequently utilized in much of the US and Europe. In our opinion, this is likely due to a combination of: a lack of physician awareness, potentially due to the fact that gastroenterologists do not traditionally treat infectious diseases; dissatisfaction with historical AST services; and difficulties with reimbursement (4).

Identification of patient or clinical risk factors for resistance could be beneficial in minimizing the prescription of unnecessary antibiotics. In this study, the proportion of patients that were female was significantly higher in those with clarithromycin-resistant isolates than susceptible isolates (69.7% vs 60.5%, $P < 0.05$). Similarly, a study in Alaska of isolates taken between 2000 and 2016 reported that metronidazole- and clarithromycin-resistant strains (42.8% and 29.8% of isolates, respectively) were more common among women (12). In the current study, the proportion of patients that were white and non-white differed between clarithromycin-resistant and susceptible isolates ($P < 0.05$). There were no significant differences in the distribution of smokers and alcohol-users between resistant and non-resistant isolates in this study; smoking has previously been associated with the acquisition of metronidazole resistance in patients with *H. pylori* infection (26). Overall, available findings from previous studies have not indicated consistent risk factors for *H. pylori* antibiotic resistance. A study from Turkey investigating the effect of patient factors on resistance, found that diabetes mellitus and prior use of metronidazole and clarithromycin were associated with increased resistance to these antibiotics. It found no association between age, sex, body mass index, smoking or alcohol use and resistance (27). A Chinese study also found that age and sex had no impact on metronidazole or amoxicillin resistance. However, it found lower clarithromycin resistance in adults younger than 40 than in those older than 40 (28).

A limitation of this study is the way in which data were collected and analyzed in an exploratory manner via descriptive comparisons, as the participants were participating in a large clinical trial not primarily designed to assess resistance. Some additional data that could have been beneficial to our understanding of the characteristics associated with resistance were not collected, such as symptoms and previous antibiotic consumption. We did not test for resistance to some other antibiotics that may be used as part of treatment regimens for *H. pylori* infection, including levofloxacin, tetracycline and rifabutin. However, recent data suggest that, in both the US and Europe, resistance to tetracycline and rifabutin is low to non-existent (15). An additional limitation of this study was that some subgroups were small, limiting interpretation; e.g., there were only 8 participants from the UK. Furthermore, overall, only 11 participants had isolates that were resistant to amoxicillin. Similarly, the relatively small number of samples from individual states and countries are probably not generalizable to a specific provider's region of practice. Rather, this information provides estimates of the point prevalence of resistance that should reinforce general concepts around preferred treatment regimens, antibiotic stewardship, and the need for AST on a broader scale.

Overall, these data provide robust evidence to support a shift away from the default empiric prescription of triple combinations containing a PPI and clarithromycin for *H. pylori* infection in the US and Europe, and a shift towards more responsible antibiotic stewardship.

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Study Highlights

WHAT IS KNOWN

✓ Guidelines recommend that local resistance rates to commonly used antibiotics including clarithromycin determine treatment choice for *H. pylori* infection.

✓ Up-to-date information on resistance rates is limited, particularly in the US.

WHAT IS NEW HERE

✓ The prevalence of clarithromycin and metronidazole resistance in *H. pylori* isolates was higher than previously reported.

✓ The empiric use of proton pump inhibitor-based triple therapy containing clarithromycin should be abandoned.

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