

Risk Factors for *Helicobacter pylori* Resistance in the United States: The Surveillance of *H. pylori* Antimicrobial Resistance Partnership (SHARP) Study, 1993–1999

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Background: Pretreatment antimicrobial resistance has an important impact on the efficacy of many *Helicobacter pylori* treatment regimens.

Objective: To estimate the prevalence of *H. pylori* resistance to antimicrobials in the United States, to characterize risk factors associated with *H. pylori* antimicrobial resistance, and to explore the association between drug utilization and antimicrobial resistance patterns over time.

Design: Meta-analysis using patient-level data.

Setting: 20 nationwide trials of *H. pylori* eradication.

Patients: 3624 men and women, each of whom contributed one isolate.

Measurements: Rates of *H. pylori* resistance to clarithromycin, metronidazole, and amoxicillin, according to geographic region, age, sex, study year, ethnicity, ulcer status, test method, and study.

Results: Overall resistance to clarithromycin, metronidazole, and amoxicillin was 10.1% (95% CI, 9.1% to 11.1% [360 of 3571

patients]), 36.9% (CI, 35.1% to 38.7% [1063 of 2883 patients]), and 1.4% (CI, 1.0% to 1.8% [48 of 3486 patients]), respectively. In multivariable analyses, multiple risk factors were associated with resistance to individual agents. Clarithromycin resistance was significantly associated with geographic region ($P = 0.050$), older age ($P < 0.001$), female sex ($P < 0.001$), inactive ulcer disease ($P < 0.001$), and study ($P = 0.010$). Metronidazole resistance was significantly associated with female sex ($P < 0.001$), earlier year of study enrollment ($P = 0.036$), Asian ethnicity ($P < 0.001$), use of an epsilometer test ($P = 0.002$), and study ($P < 0.001$). Amoxicillin resistance was low and was not significantly associated with any risk factor. In the 1990s, when rates for use of oral macrolides and metronidazole were relatively stable, clarithromycin resistance rates were stable and metronidazole resistance rates varied.

Conclusions: Clinicians should consider risk factors for antimicrobial resistance when deciding which patients should have susceptibility testing and when choosing appropriate *H. pylori* treatments in the empirical setting.

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H*elicobacter pylori* is the major pathologic agent in the development of gastric and duodenal ulcers, and *H. pylori* eradication is known to reduce recurrence of peptic ulcers (1). In addition, infection has been linked to chronic active gastritis, gastric carcinoma, mucosa-associated lymphoid-tissue lymphoma, and possibly nonulcer dyspepsia. Pretreatment antimicrobial resistance has an important negative impact on the efficacy of many *H. pylori* treatment regimens. Although researchers have attempted to evaluate *H. pylori* resistance in the United States (2–4), risk factors associated with antimicrobial resistance have not been well characterized. Identification of such risk factors is of particular interest in *H. pylori* infection, for which treatment is usually prescribed without knowledge of the susceptibility of the individual patient's isolate.

Using patient-level data, we performed a meta-analysis to estimate the prevalence of *H. pylori* resistance to

clarithromycin, metronidazole, and amoxicillin in the United States. The data were obtained from patients with ulcers who were enrolled in clinical trials between 1993 and 1999. We also attempted to characterize risk factors associated with antimicrobial resistance to *H. pylori* and explored the association between drug use and antimicrobial resistance patterns over time.

METHODS

The U.S. Food and Drug Administration (FDA) invited pharmaceutical companies that had *H. pylori* development programs to assist in developing a program for evaluating pretreatment *H. pylori* antimicrobial resistance in patients with ulcers. The study was called the Surveillance of *H. pylori* Antimicrobial Resistance Partnership (SHARP). The pharmaceutical companies provided information that had previously been submitted

to support a new drug application or was obtained from other in-house data.

The FDA requested the following data: study number, patient identification number, date of culture, state in which the patient was enrolled, age, sex, ethnicity, ulcer status (active vs. inactive ulcer at baseline), method used to test for clarithromycin susceptibility, pretreatment clarithromycin minimal inhibitory concentration (MIC), method used to test for metronidazole susceptibility, pretreatment metronidazole MIC, method used to test for amoxicillin susceptibility, and pretreatment amoxicillin MIC.

For our study, we included trials in which isolates were collected from patients with active or inactive peptic ulcer disease. According to study protocol, an active ulcer was defined endoscopically as a break in the mucosa of greater than 3 mm. Patients were considered to have inactive ulcers if they had had ulcer disease (confirmed with endoscopy or radiography) in the past 5 years. We included only trials that enrolled patients in the United States or Puerto Rico.

Susceptibility testing was performed at one of two major laboratories with expertise in culturing *H. pylori* (Veteran Affairs Medical Center–Baylor College of Medicine and Microbiology Specialists, Inc., both in Houston, Texas). At least one MIC value obtained by agar dilution or epsilometer test (also called E-test) had to be reported for clarithromycin, metronidazole, or amoxicillin. We used only one isolate from each patient for our analysis. When MIC results were available for antrum and corpus biopsy specimens, the higher of the two values was selected. In 1 of the 20 included trials, susceptibility testing was performed by both agar dilution and E-test. In 106 patients, MIC results were available by both methods for all three drugs. For these patients, only results obtained by agar dilution were included because agar dilution is the testing method preferred by the National Committee for Clinical Laboratory Standards (NCCLS).

The NCCLS interpretative criteria for agar dilution were used to classify the susceptibility of isolates to clarithromycin. An MIC less than or equal to 0.25 $\mu\text{g}/\text{mL}$ indicated susceptibility, and an MIC of at least 1 $\mu\text{g}/\text{mL}$ indicated resistance (5). The E-test strip allows MICs that may not correspond to standard twofold dilutions obtained by agar dilution; therefore, the criterion for intermediate susceptibility by agar dilution was modified

from 0.5 $\mu\text{g}/\text{mL}$ to a range of greater than 0.25 $\mu\text{g}/\text{mL}$ to less than 1 $\mu\text{g}/\text{mL}$.

Because the NCCLS has not set interpretative criteria for susceptibility of *H. pylori* isolates to metronidazole, we used NCCLS criteria for anaerobes; an MIC less than or equal to 8 $\mu\text{g}/\text{mL}$ indicated susceptibility and an MIC of at least 32 $\mu\text{g}/\text{mL}$ indicated resistance. This resistance breakpoint has been correlated with treatment failures in patients receiving clarithromycin, metronidazole, and omeprazole (6). The intermediate category was modified from 16 $\mu\text{g}/\text{mL}$ to a range of greater than 8 to $\mu\text{g}/\text{mL}$ to less than 32 $\mu\text{g}/\text{mL}$. This allowed us to correlate E-test values with values obtained by agar dilution. In the analysis of resistance rates by risk factor, we did not use an intermediate category for clarithromycin or metronidazole. Isolates that fell into the intermediate range were classified as susceptible.

A resistance breakpoint for amoxicillin has not been determined. Isolates were considered susceptible if the MIC was less than or equal to 0.25 $\mu\text{g}/\text{mL}$ (7) and were considered resistant if the MIC exceeded 0.25 $\mu\text{g}/\text{mL}$. In two trials, ampicillin was used in place of amoxicillin for susceptibility testing with the E-test. Ampicillin and amoxicillin are generally considered to behave the same way in vitro, and the NCCLS states that ampicillin is considered the class representative for amoxicillin and ampicillin (5).

Differences in resistance rates between agar dilution and the E-test were assessed by using the chi-square test. Relationships between individual risk factors and antimicrobial resistance were assessed by using the Pearson chi-square test, the Fisher exact test (using Monte Carlo estimation), and the Wald test from univariate logistic regression models for the continuous variables (age and year).

Meta-analysis was used to combine information about the relationship between *H. pylori* resistance and eight risk factors (geographic region, age, sex, year of enrollment, ethnicity, ulcer status, test method, and study). A fixed-effects model was implemented by fixed-effects multivariable logistic regression with an indicator variable for study in all regression models. In the full multivariable model, significance was defined as a *P* value less than 0.05. Method of susceptibility testing was included in the model because of the recognized difference in results for metronidazole between the E-test

and agar dilution. Study-by-covariate interactions were examined and found to be nonsignificant ($P > 0.2$). Odds ratios and 95% CIs were calculated from the multivariable logistic regression models. These odds ratios allowed us to compare differences between levels of each risk factor while controlling for all other variables of interest. The odds ratio for age was calculated per 10 years of life (for example, 40 years vs. 30 years), and the odds ratio for year was calculated in steps of 1 year (for example, 1994 vs. 1993).

Since unadjusted proportions can be confounded by many factors, we calculated predicted rates of antimicrobial resistance in an attempt to standardize for a reference or “average” patient. The full multivariable logistic regression models were used to predict resistance rates and associated 95% CIs for each level of each risk factor. An “average” patient was assumed to be a 48-year-old white man from the southwestern United States with an active ulcer who was seen in 1996 in study 11 and whose isolate was tested by using agar dilution. Risk factors for the “average” (reference) patient were selected on the basis of the subpopulation with the largest sample size for geographic region, sex, ethnicity, ulcer status, and test method. The mean age and median year of enrollment were used. We also selected a reference study, which included the greatest number of patients who had the other reference demographic risk factors.

Predicted relative risks were calculated from the predicted resistance rates for clarithromycin and metronidazole. The predicted resistance rates for age in patients younger than 40 years, 40 to 65 years, and older than 65 years were based on a 35-year-old patient, a 48-year-old patient, and a 70-year-old patient, respectively. The predicted relative risk for age was calculated by comparing a 58-year-old patient with a 48-year-old patient, and the predicted relative risk for year was calculated by comparing 1997 with 1996.

For amoxicillin, relative risks were not calculated. The odds ratio was a good estimate of the relative risk because the overall resistance rates for amoxicillin are low. Odds ratios could not be calculated by geographic region for amoxicillin because no cases of resistance were reported in the northeastern United States. With the exception of the risk factor under consideration, all of the covariates were fixed at the previously described levels for prediction. Since results for the predicted rates and

predicted relative risks were standardized to the specified “average” patient, a selection of different covariate patterns may have produced different prediction results.

The parametric bootstrap (8) was used to estimate 95% CIs around the predicted relative risks. Ten thousand bootstrap samples were taken from a multivariate normal distribution. The mean vector was given by the maximum likelihood estimators of the regression coefficients, and the covariance matrix was given by the estimated covariance matrix of the regression coefficients, both from the full multivariable logistic regression model. The percentile method was then used to calculate 95% CIs. The 95% CI around the predicted relative risk can also be thought of as a 95% posterior, or credible, interval if it is assumed that the prior distribution for each regression coefficient is noninformative (9–11).

Univariate analyses were conducted by using JMP statistical software, version 3.2.5 (SAS Institute, Inc., Cary, North Carolina). Multivariable analyses were conducted by using SAS, version 6.12 (SAS Institute, Inc.). Bootstrap calculations were performed by using S-PLUS 2000 (MathSoft, Inc., Cambridge, Massachusetts).

To evaluate the relationship between *H. pylori* resistance to clarithromycin or metronidazole and oral antimicrobial use in the general population, information from the IMS Health database was analyzed. IMS Health Incorporated (Plymouth Meeting, Pennsylvania) is a proprietary data collecting company that uses drug utilization data to monitor trends and use of pharmaceuticals. By using combined data from Provider Perspective and Retail Perspective Online (IMS Health), IMS Health provided the projected total number of extended units (for example, the number of individual tablets or capsules) of solid oral formulations of macrolides (erythromycin, clarithromycin, and azithromycin) and metronidazole purchased by “specific channels” in the United States from 1994 through 1999. Data from 1993 were not available for comparison. Specific channels in the combined database included independent pharmacies, chain pharmacies, mass merchandisers with and without pharmacies, proprietary stores (without pharmacies), food stores with pharmacies, nonfederal hospitals, federal facilities, clinics, and long-term care facilities.

Participating companies supplied the FDA with susceptibility data from previously conducted clinical trials. No funding was obtained for this study.

Table 1. Summary of Clinical Trials Included in the Analysis*

Study Number (Reference)	Patients <i>n</i>	States	Regions	Year	Mean Age (Range) <i>y</i>	Sex	
						Male	Female
						%	
1 (12)	182	21	C, MA, MW, NE, NW, P, S, SE, SW	1993–1994	50 (20–84)	67	33
2 (12)	187	16	C, MA, MW, NE, NW, P, S, SE, SW	1993–1994	47 (18–77)	70	30
3 (13)	70	12	C, MW, NE, NW, S, SE, SW	1994	48 (26–73)	76	24
4 (14)	185	21	C, MA, MW, NE, NW, S, SE, SW	1994–1995	47 (20–80)	71	29
5 (15)	283	25	C, MA, MW, NE, NW, P, S, SE, SW	1994–1995	51 (22–84)	72	28
6 (16)	240	25	C, MA, MW, NE, NW, P, S, SE, SW	1995–1996	47 (22–81)	65	35
7 (15)	223	21	C, MA, MW, NE, NW, P, S, SE, SW	1995–1996	48 (19–78)	71	29
8 (15)	123	22	C, MA, MW, NE, NW, P, S, SE, SW	1996	51 (20–77)	64	36
9 (17)	144	13	C, MA, P, S, S, SW	1996	48 (22–82)	67	33
10 (17)	129	17	C, MA, NE, NW, P, S, SE, SW	1996	46 (22–86)	67	33
11 (18)†	131	20	C, MA, MW, NE, NW, S, SE, SW	1996	49 (21–84)	68	32
12 (17)	167	21	C, MA, MW, NE, NW, P, S, SE, SW	1996	52 (20–82)	59	41
13 (19)	50	14	C, MW, NE, NW, P, S, SE, SW	1996–1997	53 (24–85)	64	36
14 (20)	218	21	C, MA, MW, NE, NW, P, S, SE, SW	1997–1998	47 (18–86)	61	39
15 (20)	70	21	C, MA, MW, NE, NW, S, SE, SW	1997–1998	53 (18–87)	41	59
16 (4)	413	23	C, MA, MW, NE, NW, P, S, SE, SW	1997–1999	49 (18–83)	65	35
17 (21)	50	12	C, MA, NE, S, SE, SW	1998	49 (26–77)	68	32
18 (21)	311	29	C, MA, MW, NE, NW, P, S, SE, SW	1998–1999	48 (19–78)	64	36
19 (21)	82	10	C, MA, MW, NE, NW, S, SE, SW	1998–1999	40 (21–70)	60	40
20 (4)	366	26	C, MA, MW, NE, NW, P, S, SE, SW	1998–1999	46 (20–84)	64	36

* C = Central; MA = mid-Atlantic; MW = Midwest; NE = Northeast; NW = Northwest; P = Great Plains; S = South; SE = Southeast; SW = Southwest.

† In this trial, susceptibility testing for all three drugs was performed by both E-test and agar dilution. In 106 patients, for whom results from both methods were available, only the results from agar dilution were included.

RESULTS

Susceptibility

We compiled susceptibility data from 20 nationwide clinical trials conducted by six pharmaceutical companies from 1993 to 1999. The study characteristics of each trial are summarized in Table 1 (4, 12–21). Predicted antimicrobial resistance rates by study for the 20 included trials are shown in Figure 1. Eradication results from 12 of these 20 studies have been published elsewhere (4, 13, 14, 16–18, 21). Overall, isolates from 4018 patients were collected. Isolates with at least one MIC value reported were available from 3624 patients (90%).

The in vitro susceptibilities to clarithromycin, metronidazole, and amoxicillin overall and according to test method (agar dilution or E-test) are listed in Table 2. Overall resistance to clarithromycin, metronidazole, and amoxicillin was 10.1% (95% CI, 9.1% to 11.1% [360 of 3571 patients]), 36.9% (CI, 35.1% to 38.7% [1063 of 2883 patients]), and 1.4% (CI, 1.0% to 1.8% [48 of 3486 patients]), respectively. Results for clarithromycin resistance were similar with either method. However, metronidazole resistance was significantly higher with the E-test than with agar dilution (22 percentage points

[CI, 18.5 to 25.5 percentage points]; $P < 0.001$). The E-test was used for metronidazole in trials that enrolled patients from 1994 to 1996. In 1993 and from 1997 to 1999, only agar dilution was used. When we analyzed only the 3 years in which E-testing was performed, the results for agar dilution did not change (25.8% [126 of 489 patients]). The difference in resistance rates between the two testing methods was 0.7 percentage points (CI, –0.1 to 1.7 percentage points), which bordered on significance for amoxicillin ($P = 0.054$).

Risk Factor Analyses

For each of the eight risk factors, we present unadjusted and predicted antimicrobial resistance rates for an “average” patient (Table 3). P values are presented for the full multivariable model. Predicted resistance rates for clarithromycin and metronidazole were lower than the unadjusted rates for all risk factors evaluated, except year of enrollment (both drugs) and use of the E-test (metronidazole). In contrast, for amoxicillin, predicted resistance rates were higher than unadjusted rates for all risk factors. Given the low overall rates of amoxicillin resistance, the predicted resistance rates may have been

Table 1—Continued

	Ethnicity					Ulcer Status		Susceptibility Test			Laboratory
	Asian	Black	Hispanic	White	Other	Active	History	Clarithromycin	Metronidazole	Amoxicillin	
	← % →										
3	24	0	69	4	100	0	Agar	Agar	Agar	A	
1	33	0	54	12	100	0	Agar	Agar	Agar	A	
7	23	10	60	0	100	0	E-test	E-test	E-test	A	
2	25	7	65	1	86	14	E-test	E-test	E-test	B	
7	21	6	64	2	81	19	E-test	E-test	E-test	B	
2	25	16	53	4	89	11	E-test	E-test	E-test	B	
3	22	12	60	3	0	100	E-test	E-test	E-test	B	
8	18	11	63	0	81	19	E-test	E-test	E-test	B	
1	23	0	76	0	100	0	E-test	E-test	E-test	A	
2	29	0	67	2	100	0	E-test	E-test	E-test	A	
5	18	21	53	3	86	14	Agar and E-test	Agar and E-test	Agar and E-test	B	
5	22	0	49	24	0	100	Agar	Agar	Agar	A	
2	28	0	70	0	0	100	Not done	Agar	Not done	A	
3	17	0	41	39	100	0	Agar	Not done	Agar	A	
0	9	0	61	30	0	100	Agar	Not done	Not done	A	
3	17	25	52	3	73	27	Agar	Agar	Agar	A	
0	44	0	54	2	74	26	Agar	Not done	Agar	A	
3	25	0	70	2	79	21	Agar	Not done	Agar	A	
2	30	0	66	2	91	9	Agar	Not done	Agar	A	
2	28	24	45	1	78	22	Agar	Agar	Agar	A	

less precise in the multivariable model; therefore, relative risks were not calculated for amoxicillin.

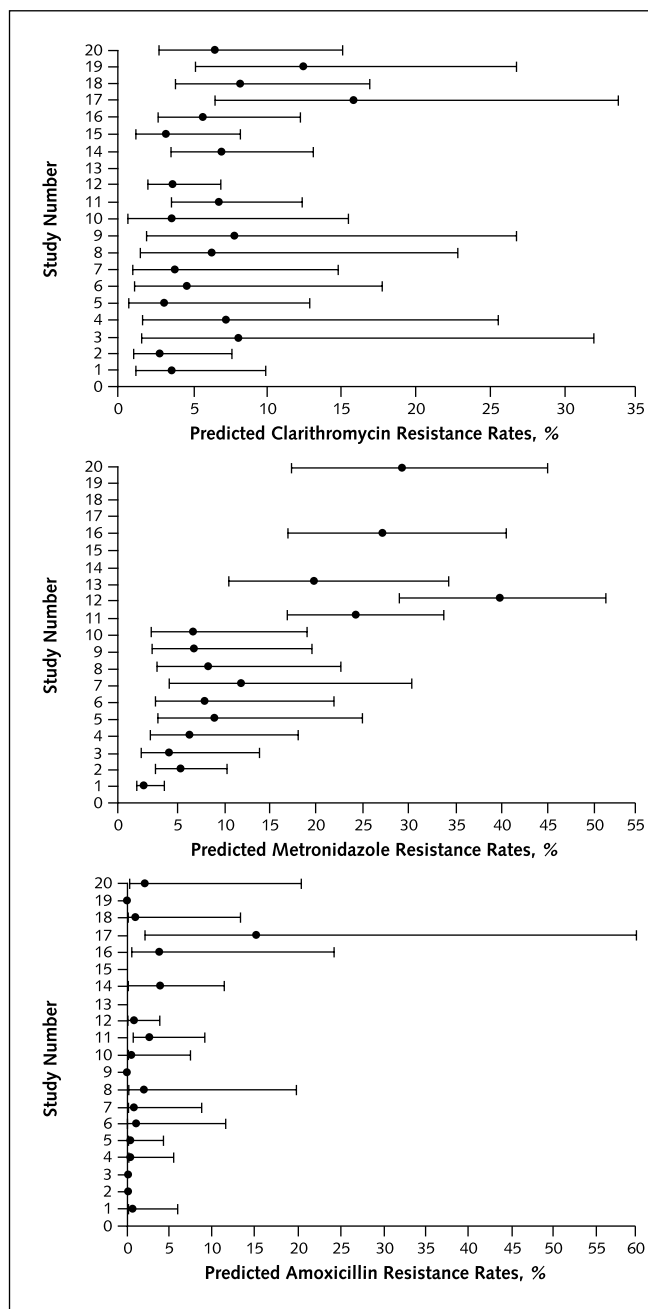
In univariate analyses, significant differences in clarithromycin resistance were seen for the following risk factors: geographic region ($P = 0.014$), age ($P < 0.001$), sex ($P < 0.001$), year of enrollment ($P = 0.003$), ulcer status ($P < 0.001$), and study ($P = 0.004$). In the multivariable model, clarithromycin resistance varied significantly by geographic region and by study (Table 3). The highest resistance rates, 13.9% and 13.0%, occurred in the mid-Atlantic and northeastern regions of the United States, respectively. For the mid-Atlantic region, the relative risk was 3.1 (CI, 1.2 to 8.8) and the odds ratio was 3.4 (CI, 1.2 to 9.8). For the northeastern region, the relative risk was 3.4 (CI, 1.2 to 9.9) and the odds ratio was 3.7 (CI, 1.3 to 11.2). The Great Plains region seemed to influence regional differences in resistance rates, but region retained its significance when the Great Plains were excluded from the model. Clarithromycin resistance was also significantly more likely in older patients, women (relative risk, 1.6 [CI, 1.3 to 2.0]; odds ratio, 1.7 [CI, 1.4 to 2.2]), and patients with an inactive ulcer (relative risk, 1.9 [CI, 1.4 to 2.5]; odds ratio, 2.0 [CI, 1.5 to 2.8]).

In univariate analyses, metronidazole resistance was significantly associated with geographic region ($P =$

0.042), age ($P = 0.002$), sex ($P < 0.001$), ethnicity ($P < 0.001$), ulcer status ($P < 0.001$), test method ($P < 0.001$), and study ($P < 0.001$). Metronidazole resistance rates varied significantly among geographic regions; unadjusted rates ranged from 29.5% in the mid-Atlantic region to 40% in the southeastern United States. In the multivariable model, metronidazole resistance was significantly associated with female sex (relative risk, 1.7 [CI, 1.5 to 2.0]; odds ratio, 2.0 [CI, 1.9 to 2.8]), Asian ethnicity (relative risk, 1.9 [CI, 1.5 to 2.6]; odds ratio, 2.8 [CI, 1.8 to 4.5]), earlier year of enrollment, E-test use, and study. When we analyzed resistance rates by both age and sex, metronidazole resistance rates were highest (52% [CI, 45.6% to 58.2%]) in women younger than 40 years of age (132 of 254 patients). In comparison, metronidazole resistance was 47% (CI, 43.3% to 50.8% [330 of 701 patients]) in women at least 40 years of age, 32.4% (CI, 28.5% to 36.5% [179 of 553 patients]) in men younger than 40 years of age, and 30.7% (CI, 28.2% to 33.2% [423 of 1380 patients]) in men at least 40 years of age.

Year was a significant factor in the multivariable model for metronidazole; however, the rates were highly variable over time. Resistance was highest during the years when the E-test was used (1994–1996). Thirty-two percent (130 of 407 patients), 100% (623 of 623

Figure 1. Predicted antimicrobial resistance rates by study.



Error bars represent 95% CIs.

patients), and 67% (659 of 977 patients) of the data for 1994, 1995, and 1996, respectively, were derived from E-test results. Unadjusted resistance rates for metronidazole were 10.1% (28 of 277 patients) in 1994 and

42.1% (134 of 318 patients) in 1996 with agar dilution only and 43.1% (56 of 130 patients) in 1994, 51.2% (319 of 623 patients) in 1995, and 46.1% (304 of 659 patients) in 1996 with the E-test only. In 1995, no results were reported for agar dilution.

Amoxicillin resistance was low overall. In univariate analyses, resistance rates varied significantly only by study ($P = 0.002$). In the multivariable model, none of the covariates was significantly associated with amoxicillin resistance.

Simultaneous resistance to clarithromycin and metronidazole was also investigated. A total of 2832 isolates were tested for susceptibility to both clarithromycin and metronidazole, and 110 of 2832 (3.9% [CI, 3.2% to 4.7%]) had dual resistance. Multivariable analysis showed that resistance to both agents was significantly associated with sex ($P < 0.001$), age ($P = 0.001$), year ($P = 0.094$), ethnicity ($P = 0.03$), and study ($P = 0.069$). The dual-resistance rate was 6.9% in women (65 of 936 patients), 2.4% in men (45 of 1896 patients), 2.3% in patients younger than 40 years of age (18 of 794 patients), and 4.5% in patients at least 40 years of age (92 of 2038 patients). Dual-resistance rates increased from 0% (0 of 92 patients) in 1993 to 5.4% (50 of 932 patients) in 1996 and then decreased again to 2.1% (4 of 187 patients) in 1999. Asian persons had the highest rate of dual resistance (8.0% [8 of 100 patients]), while patients whose ethnicity was classified as “other” had the lowest rate of dual resistance (0.86% [1 of 116 patients]). Dual-resistance rates varied by study, from 0% (0 of 182 patients) to 6.9% (10 of 144 patients).

Utilization Data

During the 1990s, when rates of oral macrolide and metronidazole use were relatively stable, clarithromycin resistance rates were stable and metronidazole resistance rates varied (Figure 2). The slight downward trend in purchase of macrolide units between 1995 and 1998 was driven by the decreasing use of erythromycin. Use of the newer macrolides, clarithromycin and azithromycin, which require less frequent dosing and fewer tablets per treatment course, remained constant or increased over the same time period, respectively.

DISCUSSION

Pretreatment antimicrobial resistance of *H. pylori* has been found to have a negative impact on treatment

Table 2. In Vitro Susceptibility of *Helicobacter pylori* Isolates Collected between 1993 and 1999*

Agent	Patientst	MIC ₅₀	MIC ₉₀	Range	Susceptible Isolates	Intermediate Isolates	Resistant Isolates
	n	← μg/mL →			← % →		
Clarithromycin	3571	0.03	1.0	0.004 to >256	89.2	0.7	10.1
Agar dilution	2152	0.03	2.0	0.004 to >256	89.3	0.2	10.6
E-test	1419	0.03	0.38	0.016 to >256	89.1	1.6	9.4
Metronidazole	2883	4	>32	≤0.002 to >256	57.7	5.4	36.9
Agar dilution	1471	2	64	0.012 to >256	68.0	5.9	26.1
E-test	1412	16	>32	≤0.002 to >256	46.9	5.0	48.1
Amoxicillin	3486	≤0.016	0.06	<0.016 to >256	98.6	–	1.4
Agar dilution	2070	0.016	0.06	<0.016 to 16	98.9	–	1.1
E-test	1416	≤0.016	0.06	<0.016 to >256	98.2	–	1.8

* MIC = minimal inhibitory concentration. Breakpoints used to define susceptible, intermediate, and resistant categories are as follows. Clarithromycin: ≤0.25 μg/mL = susceptible, >0.25 to <1 μg/mL = intermediate, ≥1 μg/mL = resistant; metronidazole: ≤8 μg/mL = susceptible, >8 to <32 μg/mL = intermediate, ≥32 μg/mL = resistant; amoxicillin: ≤0.25 μg/mL = susceptible, >0.25 μg/mL = resistant.

† In 106 patients, susceptibility testing for all three drugs was performed by both E-test and agar dilution. Only the results from agar dilution were included.

efficacy (22, 23). Clarithromycin resistance seems to be the most compromising factor. Resistance reduces treatment efficacy by an average of 55.4% (CI, 33.2% to 77.6%), as determined by meta-analytic methods (24). However, all regimens may not be equally affected. Data from FDA-approved regimens show that resistance has the greatest effect on dual therapy with clarithromycin and an antisecretory agent; such therapy fails in 95.1% of patients (39 of 41) with resistant pretreatment isolates (7). Although triple-drug therapies are less affected, they also fail in 68.6% of patients (24 of 35) with resistant pretreatment isolates (7).

Pretreatment resistance to metronidazole does not always predict decreased clinical efficacy (25) and is complicated by the lack of a standard in vitro method for determining susceptibility. However, two recent meta-analyses showed that pretreatment metronidazole resistance predicts poor outcome after treatment with a metronidazole-containing regimen (24, 26). In one analysis, which examined all metronidazole-containing regimens (24), resistance was found to reduce effectiveness by an average of 37.7% (CI, 29.6% to 45.7%). In the second analysis (26), nitroimidazole-containing triple-therapy regimens achieved 90% eradication in patients with susceptible strains but less than 75% eradication in patients with resistant strains. Only quadruple-therapy regimens (a proton-pump inhibitor, bismuth, tetracycline, and metronidazole) given for at least 1 week were equally effective in treating metronidazole-susceptible and metronidazole-resistant strains (92% [range, 63% to 100%]).

Amoxicillin resistance is rare but has been associated with a reduction in the efficacy of dual therapy with omeprazole and amoxicillin (27). The clinical relevance of amoxicillin resistance in triple-therapy regimens has not been studied.

The NCCLS has only recently standardized methods, including medium, inoculum, and incubation, for testing the susceptibility of *H. pylori* to clarithromycin. Agar dilution is the preferred method (5). Testing conditions, including choice of medium, age of the colonies, incubation period and conditions, and inoculum size, have been shown to influence results of tests for susceptibility to metronidazole (28, 29). It is recognized that E-test results for metronidazole do not always correlate with those of agar dilution (6, 30). In the United States, the overall rate of metronidazole resistance was found to be 39% (690 of 1768 isolates) by E-test and 25.7% (317 of 1234 isolates) by the NCCLS agar dilution method (30). Data gathered in Europe from a large multinational, multicenter randomized clinical trial showed that 36% of isolates (171 of 469) were resistant to metronidazole on E-test and 29% (136 of 469) were resistant on agar dilution; the criterion for resistance was an MIC value greater than 8 μg/mL. Of the 333 isolates classified as susceptible to metronidazole on agar dilution, 72 (22%) were resistant on the E-test (6). Conversely, MIC results obtained for clarithromycin seemed to be similar for both methods (6, 31). E-test MIC values for amoxicillin have been reported to be within one- to twofold of MIC values on agar dilution (31). In our

Table 3. Factors Associated with *Helicobacter pylori* Resistance*

Factor	Clarithromycin				P Value†	Metronidazole	
	Unadjusted Resistance Rate	Predicted Resistance Rate (95% CI)	Predicted RR (95% CI)	Adjusted OR (95% CI)		Unadjusted Resistance Rate	Predicted Resistance Rate (95% CI)
	% (n/n)	%				% (n/n)	%
Geographic region					0.050		
Northeast	13.0 (32/246)	11.5 (5.9–21.3)	3.4 (1.2–9.9)	3.7 (1.3–11.2)		31.2 (57/183)	19.4 (12.2–29.4)
Mid-Atlantic	13.9 (60/432)	10.6 (5.7–18.9)	3.1 (1.2–8.8)	3.4 (1.2–9.8)		29.5 (105/356)	20.2 (13.4–29.2)
Southeast	10.4 (72/691)	8.5 (4.5–15.5)	2.5 (0.9–6.9)	2.7 (0.9–7.7)		40.0 (221/553)	24.9 (17.2–34.5)
Central	8.5 (26/305)	7.3 (3.6–14.2)	2.2 (0.8–6.3)	2.3 (0.8–6.8)		37.7 (92/244)	22.1 (14.6–32.0)
Midwest	11.9 (39/327)	9.3 (4.7–17.5)	2.7 (1.0–7.8)	2.9 (1.0–8.6)		37.8 (104/275)	21.7 (14.2–31.7)
South	9.0 (50/558)	7.0 (3.6–13.2)	2.1 (0.8–5.8)	2.2 (0.7–6.2)		38.3 (174/454)	22.0 (14.9–31.3)
Great Plains	4.1 (4/97)	3.4 (1.0–10.4)	1.0 (referent)	1.0 (referent)		37.0 (37/100)	22.5 (13.4–35.2)
Northwest	10.0 (12/120)	8.3 (3.7–17.8)	2.4 (0.8–7.8)	2.6 (0.8–8.5)		32.1 (34/106)	16.6 (9.8–26.6)
Southwest	8.2 (65/795)	6.7 (3.5–12.4)	2.0 (0.8–5.5)	2.1 (0.7–5.9)		39.1 (239/612)	24.3 (16.9–33.8)
Age‡			1.2 (1.1–1.3)	1.2 (1.1–1.3)	<0.001		
<40 y	7.5 (77/1030)	5.5 (2.8–10.4)				38.5 (311/807)	25.7 (17.7–35.7)
40–65 y	10.5 (222/2107)	6.7 (3.5–12.4)				37.7 (648/1721)	24.3 (16.9–33.8)
>65 y	14.1 (61/434)	9.3 (4.8–17.0)				29.3 (104/355)	22.1 (15.0–31.4)
Sex					<0.001		
Female	13.5 (165/1223)	10.9 (5.8–19.7)	1.6 (1.3–2.0)	1.7 (1.4–2.2)		48.3 (461/954)	42.4 (31.4–54.2)
Male	8.3 (195/2348)	6.7 (3.5–12.4)	1.0 (referent)	1.0 (referent)		31.2 (602/1929)	24.3 (16.9–33.8)
Year§			0.9 (0.7–1.3)	1.0 (0.7–1.3)	>0.2		
1993	4.3 (4/92)	7.6 (2.4–21.7)				8.7 (8/92)	40.9 (22.4–62.4)
1994	7.8 (32/409)	7.3 (2.9–17.0)				20.6 (84/407)	35.3 (21.7–51.9)
1995	8.8 (55/625)	7.0 (3.4–13.8)				51.2 (319/623)	29.7 (20.0–41.6)
1996	10.2 (95/935)	6.7 (3.5–12.4)				44.8 (438/977)	24.3 (16.9–33.8)
1997	10.4 (22/212)	6.3 (3.0–12.8)				25.0 (2/8)	19.6 (12.5–29.3)
1998	12.0 (131/1090)	6.0 (2.3–14.5)				28.2 (166/589)	15.5 (8.3–26.9)
1999	10.1 (21/208)	5.6 (1.7–17.2)				24.6 (46/187)	12.1 (5.3–25.4)
Ethnicity					>0.2		
Asian	11.0 (13/118)	8.1 (3.5–17.5)	1.2 (0.7–2.1)	1.2 (0.8–2.1)		55.4 (56/101)	46.8 (32.4–61.8)
Black	9.3 (77/829)	5.8 (2.9–11.3)	0.9 (0.7–1.1)	0.9 (0.7–1.1)		44.6 (300/672)	37.8 (27.2–49.7)
Hispanic	8.5 (28/331)	6.8 (3.4–13.1)	1.0 (0.7–1.6)	1.0 (0.7–1.5)		43.2 (142/329)	34.9 (25.0–46.3)
White	10.8 (223/2066)	6.7 (3.5–12.4)	1.0 (referent)	1.0 (referent)		30.8 (512/1665)	24.3 (16.9–33.8)
Other	8.4 (19/227)	6.2 (2.7–13.5)	0.9 (0.6–1.6)	0.9 (0.6–1.5)		45.7 (53/116)	38.1 (25.2–52.9)
Ulcer status					<0.001		
Active ulcer	8.6 (232/2683)	6.7 (3.5–12.4)	1.0 (referent)	1.0 (referent)		34.6 (729/2105)	24.3 (16.9–33.8)
Inactive ulcer	14.4 (128/887)	12.6 (6.5–22.9)	1.9 (1.4–2.5)	2.0 (1.5–2.8)		43.0 (334/777)	22.7 (14.9–33.0)
Test method					>0.2		
Agar	10.5 (227/2152)	6.7 (3.5–12.4)	1.0 (referent)	1.0 (referent)		26.1 (384/1471)	24.3 (16.9–33.8)
E-test	9.4 (133/1419)	6.6 (1.9–20.3)	1.0 (0.3–3.4)	1.0 (0.5–2.0)		48.1 (679/1412)	61.6 (37.1–81.3)
Study	4.7 (6/129) to 24.0 (12/50)¶	2.8 (1.0–7.6) to 15.8 (6.5–33.6)**	–	–	0.010	4.4 (8/182) to 54.3 (121/223)††	1.3 (0.5–3.5) to 39.7 (29.0–51.4)‡‡

* OR = odds ratio; RR = relative risk.
 † From the full multivariable logistic regression model.
 ‡ Odds ratios for age were calculated per decade of life.
 § Odds ratios for year were calculated per year of enrollment.
 || Values are ranges for groups of studies.
 ¶ Study 10 to study 17.
 ** Study 2 to study 17.
 †† Study 1 to study 17.
 ‡‡ Study 1 to study 12.
 §§ Study 7 to study 2.
 ||| Study 5 to study 17.

analysis, results for clarithromycin resistance were similar on agar dilution and the E-test. However, metronidazole resistance was 22% higher with the E-test than with agar dilution. Although resistance rates for amoxicillin differed slightly between the two testing methods,

the difference is probably not clinically relevant since the overall rate of amoxicillin resistance is low.

In the multivariable analysis, geographic region was found to be significantly associated with clarithromycin resistance. Resistance rates were highest on the East

Table 3—Continued

Metronidazole			Amoxicillin			
Predicted RR (95% CI)	Adjusted OR (95% CI)	P Value†	Unadjusted Resistance Rate % (n/n)	Predicted Resistance Rate (95% CI) %	Adjusted OR (95% CI)	P Value†
1.0 (0.7–1.4)	1.0 (0.6–1.5)	>0.2	0 (0/237)	–	–	>0.2
1.0 (referent)	1.0 (referent)		1.9 (8/422)	2.7 (0.7–10.2)	–	
1.2 (1.0–1.6)	1.3 (1.0–1.8)		0.9 (6/670)	1.5 (0.3–6.0)	–	
1.1 (0.8–1.5)	1.1 (0.8–1.7)		2.0 (6/296)	3.2 (0.8–11.9)	–	
1.1 (0.8–1.4)	1.1 (0.8–1.6)		2.2 (7/320)	3.8 (0.9–15.0)	–	
1.1 (0.8–1.4)	1.1 (0.8–1.6)		1.1 (6/553)	1.5 (0.3–6.1)	–	
1.1 (0.8–1.7)	1.2 (0.7–1.9)		2.1 (2/97)	3.6 (0.5–19.9)	–	
0.8 (0.5–1.2)	0.8 (0.5–1.3)		2.7 (3/113)	4.3 (0.9–18.7)	–	
1.2 (0.9–1.6)	1.3 (0.9–1.8)		1.3 (10/778)	2.5 (0.7–9.0)	–	
1.0 (0.9–1.0)	0.9 (0.9–1.0)	0.084			1.0 (0.8–1.2)	>0.2
			1.4 (14/1011)	2.6 (0.7–9.8)		
			1.4 (29/2063)	2.5 (0.7–9.0)		
			1.2 (5/412)	2.3 (0.6–8.7)		
1.7 (1.5–2.0)	2.0 (1.9–2.8)	<0.001	1.6 (19/1177)	3.1 (0.8–11.5)	1.5 (1.4–1.7)	>0.2
1.0 (referent)	1.0 (referent)		1.3 (29/2309)	2.5 (0.7–9.0)	1.0 (referent)	
0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.036			0.5 (0.2–1.2)	0.128
			3.3 (3/92)	13.2 (1.1–68.2)		
			1.0 (4/407)	8.5 (1.1–43.5)		
			1.8 (11/624)	4.7 (1.0–19.6)		
			1.9 (18/937)	2.5 (0.7–9.0)		
			0.6 (1/155)	1.3 (0.2–6.2)		
			1.0 (11/1063)	0.6 (0.1–5.8)		
			0 (0/208)	0.3 (0–6.2)		
1.9 (1.5–2.6)	2.8 (1.8–4.5)	<0.001	1.7 (2/118)	2.4 (0.4–14.0)	1.0 (0.3–3.7)	>0.2
1.6 (1.3–1.8)	1.9 (1.5–2.4)		2.1 (17/822)	4.1 (1.0–15.3)	1.9 (0.9–3.9)	
1.4 (1.2–1.8)	1.7 (1.3–2.3)		0.9 (3/332)	1.8 (0.4–8.5)	0.8 (0.3–2.4)	
1.0 (referent)	1.0 (referent)		1.2 (25/2013)	2.5 (0.7–9.0)	1.0 (referent)	
1.6 (1.2–2.1)	2.0 (1.3–3.1)		0.5 (1/201)	1.3 (0.1–12.8)	0.6 (0.1–3.2)	
1.0 (referent)	1.0 (referent)	>0.2				>0.2
0.9 (0.8–1.2)	0.9 (0.7–1.2)		1.2 (32/2670)	2.5 (0.7–9.0)	1.0 (referent)	
			2.0 (16/815)	3.5 (0.8–14.0)	1.2 (0.8–1.8)	
1.0 (referent)	1.0 (referent)	0.002				>0.2
2.5 (1.5–4.1)	5.0 (1.7–14.4)		1.1 (22/2070)	2.5 (0.7–9.0)	1.0 (referent)	
–	–	<0.001	1.8 (26/1416)	4.2 (0.5–28.0)	1.4 (0.4–4.4)	
			0 (0/187) to 6.0 (3/50)§§	0.2 (0–4.2) to 15.2 (2.1–59.7)¶¶	–	0.200

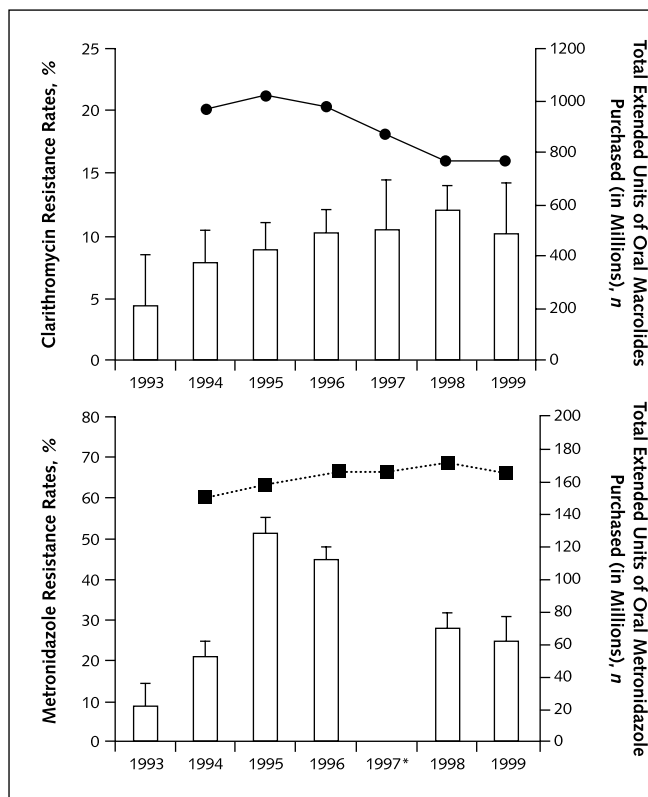
Coast (mid-Atlantic and northeast regions). It is not known why clarithromycin resistance rates differ by region. Prescribing trends for oral macrolides may have an effect, but macrolide utilization data were not available by geographic region.

Older age was shown to be significantly associated with clarithromycin resistance. Younger age seemed to be associated with metronidazole resistance on multivariable analyses, although the association was not significant. These trends may be explained by the general usage patterns for these classes of antimicrobials. Elderly patients are more likely to have respiratory tract infec-

tions, for which macrolides are commonly prescribed, and young women with gynecologic infections are likely to be treated with metronidazole. Metronidazole resistance in European countries has been found to be highest (50%) in young women 20 to 39 years of age (28). In our study, female sex was significantly associated with resistance to both metronidazole and clarithromycin in the multivariable analyses. Women younger than 40 years of age had the highest rates of metronidazole resistance. It is not clear, however, why women are more likely to be resistant to clarithromycin.

Ethnicity was a significant factor in the multivari-

Figure 2. Antimicrobial resistances rates in the United States in relation to the total number of extended units purchased.



Extended units are the number of individual tablets and capsules, as determined by IMS Health. Bars indicate resistance rates, and lines indicate the total number of extended units purchased (in millions). *The number of isolates was too small to yield a reliable estimate.

able analysis for metronidazole. White persons had a relatively low incidence of metronidazole resistance compared with persons of other ethnicities, while Asian persons had the highest incidence. Metronidazole resistance has previously been linked to ethnic origin and nationality. In an analysis of data from 11 European countries, rates of resistance to metronidazole were higher in nonwhite patients from northern Africa and from Mediterranean countries than in patients from northern European countries (28). The reason for this is unclear.

In the multivariable analysis, patients with an inactive ulcer had significantly higher antimicrobial resistance rates for clarithromycin than those who had active ulcer disease. Our database did not contain information on previous antimicrobial therapy. Recent past use of

antimicrobials (range, 2 to 8 weeks) was an exclusion criterion for all of the 20 included trials, and we were unable to determine the impact of antimicrobial use in the distant past on *H. pylori* resistance. Patients with inactive ulcer disease may have been exposed to previous unsuccessful therapies for *H. pylori* eradication; this may explain the higher rates of clarithromycin resistance in this population. However, of the 20 included trials, 17 noted previous eradication therapy as an exclusion criterion. Two trials excluded patients who had received previous treatment for *H. pylori* at any time, and 12 trials excluded patients who had recently received treatment for *H. pylori* (within 4 weeks to 1 year before enrollment). One trial specifically excluded patients who were previously treated with a metronidazole-containing regimen, and 2 trials excluded those previously treated with a macrolide-containing regimen. Despite these exclusion criteria, higher resistance rates in patients with inactive ulcer disease suggest that the prescriber should ask patients about previous antimicrobial use, especially macrolides, before selecting a treatment regimen.

Year of enrollment was not significantly associated with resistance for any of the three agents. While clarithromycin and amoxicillin resistance seemed stable between 1993 and 1999 in the multivariable analyses, metronidazole resistance tended to decrease. Although metronidazole resistance rates decreased over time, resistance was highest during the years when E-testing was used (1994–1996). Therefore, the observed changes in metronidazole resistance may not represent true changes in susceptibility in the population but may instead represent changes in in vitro testing methods over time. Resistance to metronidazole has been reported to be relatively constant in Belgium and Japan, with only a slight increase in recent years in Belgium (32, 33). Amoxicillin resistance was low overall in our analysis, so although the rates decreased over time, this finding has little clinical significance. Resistance of *H. pylori* to clarithromycin has been tracked in Belgium since 1990 and has been relatively stable overall, with a peak of 13.2% in 1997 (32). In contrast, in two regions of Japan, the prevalence of clarithromycin resistance doubled from 9.1% in 1996 to 18.7% during 1998 and 1999 (33).

To further evaluate trends of clarithromycin and metronidazole resistance over time in our population, we analyzed IMS Health data, which track antimicrobial utilization. In the setting of relatively stable rates of

overall use of oral macrolide and metronidazole antimicrobials between 1994 and 1999, *H. pylori* had stable rates of resistance to clarithromycin and variable rates of resistance to metronidazole. In addition, rates of metronidazole resistance decreased slightly between 1995 and 1999. It should be noted that these data reflect drug use in the general population and include children and persons not infected with *H. pylori*. Data on antimicrobial use for populations similar to those included in our study are not available. Even in prospective studies that ask about past antimicrobial use, this information might not be reliably collected. Nevertheless, it will be interesting to follow antimicrobial utilization in the future as macrolides are used more frequently to treat a variety of infections.

Surveillance data obtained from our large database are helpful in understanding the risk factors that predict antimicrobial resistance patterns. However, a clinical trial database does not represent a random sample of the general population, and extrapolation to general medical practice should be done cautiously. In addition, despite our efforts to control for confounding due to study differences, the possibility that the reported resistance rates may be distorted by residual confounding cannot be completely excluded. We have presented predicted antimicrobial resistance rates, in addition to the unadjusted rates, to control for confounding. We have also included both relative risks and odds ratios to characterize any disparity that might occur as resistance rates increase. However, readers should not try to generalize results for the predicted resistance rates and relative risks. Covariate patterns that differ from those of the “average” patient, as defined in our model, can produce different results.

Susceptibility information on *H. pylori* should continue to be collected to allow researchers to follow trends in antimicrobial resistance and better understand the significance of the identified risk factors. Such information will be helpful in the selection of empirical antimicrobial agents for treatment of *H. pylori* infection and may encourage the use of culture and susceptibility testing in patients at risk for resistant organisms. More detailed utilization data are needed to evaluate the effect of drug utilization on resistance over time.

In conclusion, we have identified several risk factors associated with pretreatment antimicrobial resistance. Pretreatment resistance to clarithromycin and metronidazole has a significant negative impact on treatment

efficacy. In addition, these agents are of great importance in standard treatment regimens. Therefore, clinicians should consider these risk factors when deciding which patients should have susceptibility testing and when choosing appropriate *H. pylori* treatment regimens in the empirical setting.

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References

- Hopkins RJ, Girardi LS, Turney EA. Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. *Gastroenterology*. 1996;110:1244-52. [PMID: 8613015]
- Osato MS, Reddy R, Reddy SG, Penland RL, Graham DY, Malath HM. Primary metronidazole and clarithromycin resistance rates for *Helicobacter pylori* in the U.S. [Abstract]. *Gastroenterology*. 2000;118(Suppl):A500.
- Weissfeld A, Haber M, Rose P, Kids S, Siejman N. Geographical distribution in the United States of primary resistance to clarithromycin and metronidazole in patients infected with *Helicobacter pylori* [Abstract]. *Gastroenterology*. 1997;112:A328.
- Laine L, Malone T, Bochenek W, Wang W, Osato M. Current U.S. rates of *H. pylori* antibiotic resistance and factors predicting resistance: results from ongoing trials at 77 sites [Abstract]. *Gastroenterology*. 1999;116(Suppl):A228.
- Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard—5th ed. Supplemental tables. NCCLS document M7-A5. National Committee for Clinical Laboratory Standards. Wayne, PA: National Committee for Clinical Laboratory Standards; 2000.
- Mégraud F, Lehn N, Lind T, Bayerdörffer E, O'Morain C, Spiller R, et al. Antimicrobial susceptibility testing of *Helicobacter pylori* in a large multicenter trial: the MACH 2 study. *Antimicrob Agents Chemother*. 1999;43:2747-52. [PMID: 10543758]
- Clarithromycin (Biaxin). Package insert. North Chicago, IL: Abbott Laboratories; 1999.
- Efron B. Bootstrap methods: another look at the jackknife. *Annals of Statistics*. 1979;7:1-26.
- Berger JO. *Statistical Decision Theory and Bayesian Analysis*. New York: Springer-Verlag; 1980.
- Tanner MA. *Tools for Statistical Inference*. 2nd ed. New York: Springer-Verlag; 1993.
- Greenhouse JB, Silliman NP. Applications of a mixture survival model with covariates to the analysis of a depression prevention trial. *Stat Med*. 1996;15:2077-94. [PMID: 8896141]
- Data on file, Abbott Laboratories, Abbott Park, Illinois.
- Laine L, Johnson E, Suchower L, Ronca P, Hwang C, Neil G. US double-blind, controlled trials of omeprazole and amoxicillin for treatment of *Helicobacter pylori*. *Aliment Pharmacol Ther*. 1998;12:377-82. [PMID: 9690729]
- Harford W, Lanza F, Arora A, Graham D, Haber M, Weissfeld A, et al. Double-blind, multicenter evaluation of lansoprazole and amoxicillin dual therapy for the cure of *Helicobacter pylori* infection. *Helicobacter*. 1996;1:243-50. [PMID: 9398875]
- Data on file, TAP Pharmaceutical Products, Inc., Deerfield, Illinois.
- Schwartz H, Krause R, Sahba B, Haber M, Weissfeld A, Rose P, et al. Triple versus dual therapy for eradicating *Helicobacter pylori* and preventing ulcer recurrence: a randomized, double-blind, multicenter study of lansoprazole, clarithromycin, and/or amoxicillin in different dosing regimens. *Am J Gastroenterol*. 1998;93:584-90. [PMID: 9576452]
- Laine L, Suchower L, Frantz J, Connors A, Neil G. Twice-daily, 10-day triple therapy with omeprazole, amoxicillin, and clarithromycin for *Helicobacter pylori* eradication in duodenal ulcer disease: results of three multicenter, double-blind, United States trials. *Am J Gastroenterol*. 1998;93:2106-12. [PMID: 9820381]
- Fennerty MB, Kovacs TO, Krause R, Haber M, Weissfeld A, Siepmann N, et al. A comparison of 10 and 14 days of lansoprazole triple therapy for eradication of *Helicobacter pylori*. *Arch Intern Med*. 1998;158:1651-6. [PMID: 9701099]
- Data on file, Procter & Gamble, Mason, Ohio.
- Data on file, Pfizer Central Research, New York, New York.
- Laine L, Fennerty MB, Osato M, Sugg J, Suchower L, Probst P, et al. Esomeprazole-based *Helicobacter pylori* eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials. *Am J Gastroenterol*. 2000;95:3393-8. [PMID: 11151867]
- Mégraud F. Resistance of *Helicobacter pylori* to antibiotics. *Aliment Pharmacol Ther*. 1997;11(Suppl 1):43-53. [PMID: 9146790]
- Graham DY. Antibiotic resistance in *Helicobacter pylori*: implications for therapy. *Gastroenterology*. 1998;115:1272-7. [PMID: 9797384]
- Dore MP, Leandro G, Realdi G, Sepulveda AR, Graham DY. Effect of pretreatment antibiotic resistance to metronidazole and clarithromycin on outcome of *Helicobacter pylori* therapy: a meta-analytical approach. *Dig Dis Sci*. 2000;45:68-76. [PMID: 10695616]
- Graham DY, de Boer WA, Tytgat GN. Choosing the best anti-*Helicobacter pylori* therapy: effect of antimicrobial resistance. *Am J Gastroenterol*. 1996;91:1072-6. [PMID: 8651150]
- Graham DY, de Boer WA, Tytgat GN. Choosing the best anti-*Helicobacter pylori* therapy: effect of antimicrobial resistance. *Am J Gastroenterol*. 1996;91:1072-6. [PMID: 8651150]
- van der Wouden EJ, Thijs JC, van Zwet AA, Sluiter WJ, Kleibeuker JH. The influence of in vitro nitroimidazole resistance on the efficacy of nitroimidazole-containing anti-*Helicobacter pylori* regimens: a meta-analysis. *Am J Gastroenterol*. 1999;94:1751-9. [PMID: 10406231]
- Results of a multicentre European survey in 1991 of metronidazole resistance in *Helicobacter pylori*. European Study Group on Antibiotic Susceptibility of *Helicobacter pylori*. *Eur J Clin Microbiol Infect Dis*. 1992;11:777-81. [PMID: 1468415]
- Van Der Wouden EJ, Thijs JC, Van Zwet AA, Kleibeuker JH. Review article: nitroimidazole resistance in *Helicobacter pylori*. *Aliment Pharmacol Ther*. 2000;14:7-14. [PMID: 10632640]
- Osato MS, Reddy R, Reddy SG, Penland RL, Graham DY. Reliable determination of metronidazole and clarithromycin susceptibility: comparison of methods and assessment of internal variability using simultaneously obtained antral and corpus biopsies [Abstract]. *Gastroenterology*. 2000;118(Suppl):A676-7.
- Osato MS, Flamm RK, Utrup LJ. *Helicobacter pylori* susceptibility testing: comparison of E-test and agar dilution methods [Abstract]. *Gastroenterology*. 1998;114(Suppl):A250.
- De Koster E, Devaster JM, Vandenborre C, De Bruyne I, Deltenre M. Ten years surveillance of *Helicobacter pylori* primary resistance to macrolides and imidazoles [Abstract]. *Gastroenterology*. 2000;118(Suppl):A495.
- Kato M, Yamaoka Y, Kim JJ, Reddy R, Asaka M, Kashima K, et al. Regional differences in metronidazole resistance and increasing clarithromycin resistance among *Helicobacter pylori* isolates from Japan. *Antimicrob Agents Chemother*. 2000;44:2214-6. [PMID: 10898707]