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Resistance patterns of refractory *H. pylori* infection in a referral center in the Delaware Valley

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Abstract

Introduction: *H. pylori* (HP) resistance is increasing in the US. Guidelines suggest treatment based on local resistance patterns, yet are poorly studied. We describe resistance patterns of the Delaware Valley.

Methods: A retrospective study of patients referred to the Hospital of the University of Pennsylvania, between 2009–2019 who underwent endoscopy for culture. Chart review identified demographics, history, endoscopic and culture results, treatment, and follow up.

Results: Of 109 patients referred for refractory HP, 90 had identified HP. Median age was 53.2 years and the majority was female (74%), with median 2 previous antibiotic courses for HP. Gastric erythema was the most common endoscopic abnormality. 65 (72.2%) were culture positive, and 45 (69.2%) were resistant to levofloxacin, 27 (41.5%) to metronidazole, and 39 (43.3%) to clarithromycin.

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Being resistant to any one of the 3 antibiotics was associated with resistance to either of the other two. There was an association with number of previous antibiotics with resistance (OR 1.74, $p < 0.05$).

We prescribed therapy to 77 patients based on susceptibility profiles, and 34 (37.8%) were cured, 14 (15.6%) underwent endoscopic surveillance, 3 (3.3%) were followed by infectious disease, and 39 (43.3%) were lost to follow up.

Conclusions: Antibiotic resistance is associated with refractory HP, and continues to rise. Culturing is associated with cure, and its use in clinical practice regarding efficacy, cost-effectiveness, and ability to minimize antibiotic resistance should be further studied. Overall follow-up is limited by loss to follow up, emphasizing the need for appropriate treatment.

Keywords

H. pylori; antibiotic resistance; culture and susceptibility

INTRODUCTION

Infection with the gram negative spiral bacterium, *Helicobacter pylori* (HP), has a worldwide prevalence of approximately 50% and is responsible for a multitude of gastrointestinal diseases, including atrophic gastritis, peptic ulcer disease, distal gastric adenocarcinoma and gastric MALT lymphomas.^{1–3} Guidelines suggest treating all known HP infections and subsequently testing for confirmation of eradication.^{4–6} Yet, treatment failure is a widespread problem, with estimates of 20–30%, due primarily to poor compliance and / or antibiotic resistance.^{1, 3, 7} Antibiotics were previously more effective, with eradication rates of approximately 90% in the 1990s, though many have argued that even 90% is suboptimal for effective therapy.⁸ Since then, HP has become increasingly resistant to clarithromycin, levofloxacin, and metronidazole and falling cure rates have prompted changes in guidelines, which are currently recommending quadruple therapy as first line.^{3, 4, 9} Guidelines suggest evaluating local resistance patterns in order to provide appropriate eradication regimens, yet resistance patterns in the US are poorly studied and largely unknown, with few recent studies identifying patterns of resistance, and two of the most prominent being over 15 years old.^{3, 4, 10, 11} Moreover, reimbursement, procedural risk, and patient preference prohibit feasibility of uniform culture guided treatment of patients.^{3, 4}

At our tertiary care referral center, we receive open access endoscopy and office consultations for culture and susceptibility testing of refractory HP patients throughout the Delaware Valley, allowing us to identify patterns of resistance among previously treated HP infected patients in our region as well as cure rates for susceptibility-informed treatment regimens (in a proportion of those referred). These data are critical to inform local practice methods to better control this World Health Organization classified class 1 carcinogen.²

METHODS

This retrospective descriptive study presents information pertaining to patients referred to the Hospital of the University of Pennsylvania (HUP), in Philadelphia, PA, between 2009–2019 who underwent endoscopy for HP culture and susceptibility testing (C&S). Patients

were identified using a laboratory information system (Cerner) database of gastric biopsies sent for C&S for suspected refractory HP. The electronic medical records of the identified patients were then reviewed for demographics, personal and familial medical history, poverty level (defined by median income level by zip code), previous antibiotic exposure, date of endoscopy, endoscopic findings, biopsy and C&S results, eventual antibiotic prescription, and follow up.

Endoscopies were performed in the absence of proton pump inhibitors, antibiotics and bismuth. Our culture biopsy protocol followed the Sydney system for both culture and histology.¹² Specimens were first obtained from all designated sites and placed directly in non-bacteriostatic saline at room temperature and transported via pneumatic tube system immediately to the clinical microbiology laboratory in order to permit rapid plating for culture. We then proceeded to take additional biopsies from the antrum and body for placement in formalin and routine preparation by the surgical pathology department for confirmation. Biopsy was considered positive if patients were found to have HP on H&E or thiazine stain. The tissue samples sent to the clinical microbiology lab where subjected to a rapid urease test, gram stain and were plated immediately for culture. The rapid urease test on tissue was reported after 30 minutes if positive and incubated overnight before reporting negative results. The gram stain was reported to be positive if curved gram-negative bacilli were seen under light microscopy. In addition, tissue specimens were cultured on Brucella blood agar plates and Martin Lewis agar plates. These plates were incubated at 35–37°C in a microaerobic environment. Plates were examined after a minimum of 5 days incubation, the plates were assessed for small, translucent colonies; HP was confirmed with positive tests for catalase, oxidase, and rapid urease. Specimens were then tested for susceptibility to levofloxacin, metronidazole and clarithromycin (Etest, bioMérieux, Marcy-l'Étoile, France).

Statistical analysis was performed using Stata/IC 15.1 (College Park, TX) and included univariable and multivariable analyses, with particular attention given to risk factors for resistance to antibiotics as a whole and individually, regimens associated with cure of resistant HP, and trends over time. This study was deemed exempt after review by the Institutional Review Board at the University of Pennsylvania.

RESULTS

Of 109 patients referred for refractory HP between 2009–2019, 83 (76.1%) were confirmed to have HP on gastric biopsy by H&E and/or thiazine staining. Seven patients (6.4%) were biopsy negative, but found to have HP on gram stain or urease testing. For these patients, we were able to confirm all available biopsy reports had evidence of inflammation, but no HP organisms were identified. The other 19 patients (17.4%) had no findings of HP despite referral for refractory HP.

The 90 patients with biopsy or gram/urease-proven HP are described in Table 1. Median age at the time of referral was 53.2 years, 13 (14%) were Hispanic or Latino, 36 (40%) were Black or African American, 28 (31%) were of white race (31%), and 14 (16%) were Asian. The majority was female (74%). At the time of referral, 25 (28%) lived in high socioeconomic areas, whereas <10% of residents lived below the poverty level.

Table 2 describes endoscopic findings of the 90 confirmed patients. The majority (52%) were endoscopically normal, while gastric erythema was the most common abnormal finding, in 36 patients (40%). They had received a median of 2 previous antibiotic courses prior to referral. Of the 90, 34 (38%) reported allergies to penicillin, fluoroquinolone, tetracycline, or metronidazole.

Of the 90 patients with confirmed HP, cultures were positive in 65 (72.2%). A total of 58 of 65 successfully cultured patients (89%) had confirmed resistance to either levofloxacin, metronidazole, or clarithromycin. In total, 45 (69.2%) of the 65 were resistant to levofloxacin, 27 (41.5%) to metronidazole, and 39 (43.3%) to clarithromycin. Of the 65, 18 patients (28%) were resistant to one antibiotic only, 27 (42%) were resistant to two antibiotics, and 13 (20%) were resistant to all three. Notably, 7 (10.7%) were not resistant to levofloxacin, metronidazole, or clarithromycin by Etest.

Local Resistance patterns

The patients with antibiotic resistant infections came from different areas within the Greater Philadelphia (Delaware River Valley) region. When comparing patients who were resistant to 0, 1, 2, or all 3 of the antibiotics tested, there was no significant difference in age at referral, ethnicity, race, gender, symptom, medical, or family history, allergy history, or poverty level according to number of resistant antibiotics.

Chi-squared testing showed being resistant to any one of the 3 antibiotics was associated with resistance to either of the other two, for each of the three tested antibiotics ($p < 0.05$ for all). Univariable analysis was notable for an association with increasing number of previous antibiotics course with confirmed resistance to any antibiotic (OR 1.74, $p < 0.05$).

Figure 1a displays the percentage of resistant isolates referred each year since 2009, demonstrating that levofloxacin and clarithromycin resistance dominate but that levofloxacin resistance is increasing. Figure 1b demonstrates that the number of persons referred with more than one resistant antibiotic continues to increase.

Treatment

After culture and as of this report, we have prescribed therapy to 77 patients (85.6%). Those not treated either were lost to follow-up, refused therapy or, given multiple previous regimens and previous non-successful courses of therapy, were given acid suppression and recommended for endoscopic surveillance at intervals.

We proposed antibiotic regimens together with twice daily proton pump inhibitor therapy according to resistance patterns. The most commonly prescribed regimens included: amoxicillin and rifabutin in 20 of the 90 referred patients (26%), bismuth, metronidazole, and tetracycline in 15 (19.5%), amoxicillin and levofloxacin in 8 (10.4%), amoxicillin and clarithromycin in 5 (6.5%), and bismuth and metronidazole in 5 (6.5%).

Among the 25 patients who were not resistant to any of the three tested antibiotics or the 7 that failed culture completely, we most frequently prescribed metronidazole (13 patients; 40.6%), bismuth (13 patients; 40.6%), tetracycline (11 patients; 34.4%), and amoxicillin (10

patients; 31.3%). In the 18 resistant to only one antibiotic, amoxicillin was prescribed in 8 patients (44.4%), metronidazole in 7 (38.9%), and bismuth in 7 (38.9%). Of the 27 resistant to two antibiotics, amoxicillin was prescribed in 18 (66.7%) and rifabutin in 14 (51.9%). Of the 13 resistant to three antibiotics, we prescribed metronidazole in 7 (53.8%), amoxicillin in 6 (46.2%), and rifabutin in 5 (38.5%). Figure 2 displays prescribed antibiotics by the number of resistant antibiotics. There was no clear regimen based on number of previous antibiotic courses taken.

On multivariable analyses of previous antibiotics used, we were more likely to prescribe rifabutin with increasing number of previous courses of antibiotics (OR 2.11, $p = 0.02$) and if the patient was resistant to levofloxacin in particular (OR 4.61, $p=0.01$).

Follow-up and cure

After evaluation of the 90 referred patients, 34 (37.8%) were confirmed cured, 14 (15.6%) were not cured and are now following with gastroenterologists using acid suppression and periodic endoscopic surveillance, 3 (3.3%) were not cured and are now following with infectious disease specialists, and 39 (43.3%) were lost to follow up, with unknown cure status.

Of 58 patients with confirmed resistance to either clarithromycin, metronidazole, or levofloxacin, 24 (41.4%) were cured after referral, 12 (20.7%) were not, the other 22 (37.9%) were lost to follow up, with unknown cure status. There were no significant demographic differences among these groups.

When evaluating those with known cure status, performing successful culture is associated with cure in logistic regression (34 of 59 cured; $p = 0.02$).

In univariable analysis, no antibiotic was significantly associated with known cure. Rifabutin was borderline statistically significantly associated with cure (OR 2.81; 95% CI 0.90–8.79, $p=0.08$)

There were two instances where we prescribed clarithromycin despite demonstrated resistance. Both patients reported allergies, one to penicillins, the other to fluoroquinolones. Both had two previous courses. For one, we prescribed clarithromycin, bismuth, and metronidazole, the other received clarithromycin and amoxicillin. Both were cured.

There were 8 instances where we prescribed metronidazole despite resistance by Etest. All of these patients received metronidazole with high-dose proton pump inhibitor. Only one of these patients was not subsequently cured.

Of the 32 people who both had received amoxicillin prior and who we prescribed amoxicillin as part of their regimen, 13 (40.6%) were cured, 5 (15.6%) were not cured, and 14 (43.8%) were lost to follow up.

DISCUSSION

Here, we present the resistance patterns of HP infection in treatment refractory patients at our US Eastern Seaboard referral center. Of 90 patients with biopsy confirmed HP, with a median of 2 previous HP eradication regimens prescribed, HP was successfully cultured on 72.2%. Of the 65 patients successfully cultured for HP, 89% were resistant to either metronidazole, clarithromycin, or levofloxacin by Etest. Significant risk factors for resistance included resistant to another antibiotic and an increasing number of previous antibiotic courses. Culture was successful in almost three-fourths of patients, and was associated with cure supporting its value in clinical practice. Overall follow-up was limited by loss to follow up. However, resistance has apparently increased since the previously noted patterns in Philadelphia prior to 2002, and is markedly higher than global estimates of resistance, though our referral-based population makes direct comparison difficult.^{10, 13}

Our findings suggest that antibiotic resistance of HP organisms does not happen in isolation to one antibiotic at a time, and that resistance is associated with previous antibiotic exposure. As such, the best chance for cure is with the first regimen, reiterating the importance of “antibiotic hygiene”- including appropriate completion of regimens. It also may be beneficial to consider culturing in order to obtain antibiotic susceptibility data to help guides the choice of a second regimen if a patient’s infection is not proven eradicated after their first course of therapy. This approach is more aggressive than suggested guidelines, which recommend testing only after a second failed treatment course.⁶ However, given the high loss to follow up, earlier susceptibility testing may be indicated, as untreated HP infection can lead to a host of negative outcomes, including ulcer disease and cancers.^{1, 2, 4} Treating effectively with appropriately selected second-line therapy may ameliorate these risks. While the cost-effectiveness of early culture and susceptibility testing is unknown, one can argue, that this cost should be balanced with the cost of repeated antibiotic courses, and their complications. Of course, HP culture is not universally available. It has long been held that HP is a fastidious organism that is difficult to culture. In contrast, using the methodology outlined and paying special attention to rapid plating onto culture media, we have shown that successful culture can be achieved almost three quarters of the time. Susceptibility data is crucial, and others have also called for national and regional data availability to guide antibiotic choices.³ Such data, as we confirm here, while not generally available, can be quite useful when obtained.¹⁴

Our finding that a large number of referred HP patients were already resistant to levofloxacin by the time of referral reinforces the concern regarding the alarming rates with which HP resistance develops including with “newer” regimens.¹³ This is a well-known phenomenon, and is reflected in the World Health Organization’s calls for research and development for new antibiotics against HP.^{15, 16}

We also add to a growing experience that rifabutin-containing regimens may be effective for resistant HP infections.^{17–19} Studies in the Netherlands, Italy, and Germany have demonstrated that rifabutin resistance is rare, and it is overall considered a third or fourth line agent.^{1, 3, 20} Rifabutin based therapies are not without side effects, however, as a reversible myelotoxicity has been described, though its reversibility and lack of association

with increased infections is notable.^{7, 21} Additionally, rifabutin must be used with caution given its importance in treating tuberculosis infections, limiting its widespread and empiric use.^{20, 22} Patients should be warned that rifabutin causes a darkening of the urine which is not of clinical concern. As such, despite the efficacy of rifabutin and high rates of antibiotic resistance, other non-rifabutin agents should be prescribed as much as possible. High dose proton pump inhibitor and rifabutin in combination have been suggested to be superior than rifabutin with standard dose proton pump inhibitor, which we prescribed to all of our rifabutin-receiving patients.^{18, 23} Finally, and in contrast to levofloxacin, metronidazole resistance in vitro may be overcome with the addition of high dose proton pump inhibitor in vivo, a known phenomenon which our experience also supports.^{24, 25}

To our knowledge, this is the first study describing a regional pattern of HP resistance in the United States and certainly the first in the Delaware Valley region of the Eastern Seaboard. Resistant HP is poorly described and cataloged in the US in general, and it is an important public health concern.⁴ In the absence of a national registry other regional centers in the United States could consider a similar review of their available data to provide comparisons across regions, in order to help facilitate antibiotic therapy for refractory HP. Routine culture has so far not been recommended, as it is not clearly beneficial over empirical rescue therapy.^{26–28} Even in our study, given that culture rate was approximately 70%, many patients would undergo an endoscopy without subsequent culture results, and culture is certainly an imperfect test. Future studies should evaluate its role in guiding treatment and subsequently decreasing future antibiotic courses, and therefore antibiotic resistance

Limitations of this study include its retrospective nature and the presence of missing and incomplete data, especially for symptoms and antibiotic regimens, given that these patients were referred from outside our institution and may have had multiple outside providers, for whom we do not have complete records. As such, we did not focus on previously taken regimens, and are unable to describe the association of resistance with prior antibiotic treatment regimens. We further are limited by small sample sizes which affect the power of any comparisons. We also do not have a control group where empirical HP rescue therapy is prescribed, to compare the value of culture to empirical treatment. The majority of our referral period is prior to the suggestion of quadruple therapy as first line eradication.^{3, 5} There were seven patients who were not able to be cultured, this may have been due to prior antibiotic exposure, but given the retrospective nature of our study, we were not able to confirm this. Of the patients without HP on endoscopy, these may also have been suppressed, and while inflammation on endoscopy suggests this is less likely, we were again unable to confirm due to limitations in availability of records. Lastly, we are a referral center, and thus while this information is helpful, it also continues to point to the need for large scale registries of community HP resistance rates.

In conclusion, we describe here our HP culture and susceptibility findings at a tertiary care referral center for refractory HP patients. In the Delaware Valley region of the Eastern US seaboard, patients referred for culture and susceptibility testing after a median of 2 prior courses of therapy harbored HP organisms resistant to clarithromycin, metronidazole and levofloxacin at very high rates. Culturing is associated with cure, and its use in clinical practice regarding efficacy, cost-effectiveness, and ability to minimize antibiotic resistance

should be further studied. Resistant HP is difficult to treat, even together with culture and susceptibility testing results. Risk factors for resistant HP include the number of previously attempted antibiotic regimens, as well as resistance to any antibiotic. Resistant HP is a public health issue, and we agree with the need for surveillance registries and local information regarding eradication regimens.

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Abbreviations:

HP	Helicobacter pylori
C&S	culture and susceptibility testing

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Figure 1.

Annual trends of resistance rates seen at our tertiary care referral center by a) antibiotic and b) number of antibiotics to which *H. pylori* are resistant

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Figure 2.

Anti-*H. pylori* antibiotics prescribed at our tertiary care referral center, by number of antibiotics patients to which *H. pylori* are resistant

Table 1.Characteristics of patients with identified *H. pylori*, n=90

	N (%)
Age at referral, years, median (IQR)	53.2 (43.8, 62.0)
Ethnicity	
Hispanic or Latino	13 (14%)
Race	
Asian	14 (16%)
Black or African American	36 (40%)
White	28 (31%)
More Than One Race	4 (4%)
Unknown	8 (9%)
Gender	
Female	67 (74%)
Poverty line of residence at time of referral	
<10% living below poverty line	25 (28%)
10–20% living below poverty line	17 (19%)
20–30% living below poverty line	7 (8%)
30–40% living below poverty line	17 (19%)
>40% living below poverty line	7 (8%)
Unknown	17 (19%)
History of gastric ulcer	9 (10%)
History of duodenal ulcer	7 (8%)
Personal history of gastric cancer	1 (1%)
Personal history of lymphoma	3 (3%)
Family history gastric cancer	10 (11%)
Previous treatment of vaginitis	14 (16%)
Previous treatment of parasites	1 (1%)
Reported allergies to penicillin, fluoroquinolone, tetracycline, metronidazole	34 (38%)
Reported allergies to penicillin	29 (32%)
Number of previous courses, median, IQR	2 (1–4)

Table 2.Endoscopic characteristics of patients with identified *H. pylori*, n=90

Normal stomach	47 (52%)
Gastric erythema	36 (40%)
Gastric ulcer	1 (1%)
Gastric outlet obstruction	1 (1%)
Atrophic appearing mucosa in stomach	2 (2%)
Nodularity in stomach	3 (3%)