Antibiotic Resistance of Helicobacter pylori Isolated from Patients after Partial Gastrectomy: A Retrospective Study

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ABSTRACT

Background: *To determine the prevalence of Helicobacter pylori infection and the antibiotic susceptibility of H. pylori in patients after partial gastrectomy.*

Methods: *Patients who underwent gastroscopy from January 2009 to November 2017 and had a history of partial gastrectomy were retrospectively enrolled in the remnant stomach group. Contemporary non-gastrectomized patients with an endoscopic diagnosis of chronic gastritis were enrolled in the non-operated stomach group. The detection of H. pylori infection was performed by culture and histology. The in vitro antimicrobial susceptibility was examined by the agar dilution method on strains from gastric biopsies.*

Results: *In this study, a total of 728 gastrectomized and 5035 non-gastrectomized patients were included. There was a significantly lower prevalence of H. pylori infection in the gastric-remnant patients (8.65%) than in the non-gastrectomized patients (17.76%) (P < .001) with the diagnostic method of culture. In the gastric-remnant patients, the H. pylori strains had resistance rates to metronidazole, clarithromycin, levofloxacin, amoxicillin, and furazolidone of 100%, 20.63%, 22.22%, 0%, and 0%, respectively. In the non-gastrectomized patients, H. pylori resistance to metronidazole, clarithromycin, levofloxacin, amoxicillin, and furazolidone was 90.49%, 24.61%, 21.70%, 0.22%, and 0.11%, respectively. Gastric-remnant patients had a significantly higher metronidazole resistance rate than non-gastrectomized patients (P = .005). Moreover, no significant changes in the resistance to 5 antibiotics were observed among the gastric-remnant patients from different age, gender, and surgical indication groups.*

Conclusion: *Patients after partial gastrectomy showed a lower prevalence of H. pylori infection. Gastric-remnant patients were more likely to harbor metronidazole-resistant H. pylori strains.*

Keywords: *Antibiotic resistance, gastrectomy, Helicobacter pylori, remnant stomach.*

INTRODUCTION

Helicobacter pylori is a gram-negative, microaerophilic spiral bacterium detected in gastric mucosa.[1] *H. pylori* infection rates ranged from 11% to 87.7% worldwide[2,3] and 39.05% in Beijing, China.[4] Spontaneous elimination of *H. pylori* can be detected in some of the patients who undergo gastrectomy, but reinfection with *H. pylori* can be caused by oral–oral, fecal–oral, and gastric–oral transmission.[5,6]

Chronic infection with *H. pylori* is a major risk factor for developing gastric cancer. It has also been linked to enhance the risk for developing remnant gastric cancer in the patients after gastrectomy.[7,8] Several studies show that the residual stomach does not increase the risk of stomach cancer,[9] and it is not necessary to eradicate *H. pylori* in patients after gastrectomy.[10] However, most researchers think that the remnant stomach is a special precancerous condition, and *H. pylori* eradication in gastric-remnant patients is as important as in non-gastrectomized patients.[6,7,11,12] It has also been reported that the eradication of *H. pylori* following endoscopic resection for stomach cancer can reduce the risk for developing metachronous cancers.[13,14] Furthermore, *H. pylori* eradication may improve possible precancerous gastric lesions such as atrophy and intestinal metaplasia of the gastric stump.[15] According to the guidelines from the Maastricht V/Florence Consensus and Asia–Pacific Consensus, *H. pylori*-positive patients who underwent gastrectomy for gastric neoplasia should be offered eradication treatment.[1,16]

Antibiotic resistance is the main challenge encountered in the eradication of *H. pylori*. In China, a study on *H. pylori* resistance published in 2019 indicated 78.0% of primary resistance for metronidazole, 31.0% for

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clarithromycin, 56.0% for levofloxacin, and 9.0% for amoxicillin.[17] Two recent European studies reported that primary resistance rates in Germany were 11.3% to clarithromycin and 13.4% to levofloxacin,[18] and resistance rates in Spain were noted for metronidazole (30.7%), clarithromycin (17.9%), levofloxacin (19.3%), and amoxicillin (0%).[19] A smaller study from the United States found that *H. pylori* resistance rates to metronidazole, clarithromycin, levofloxacin, and amoxicillin were 67.9%, 11.2%, 20.9%, and 10.7%, respectively.[20] However, few studies have reported antibiotic resistance patterns of *H. pylori* in patients following gastrectomy. The gastric pH levels, anatomy, physiology, motility, emptying, and *H. pylori* distribution are changed following gastrectomy,[6,21-24] which might affect the antibiotic resistance of *H. pylori*. It is necessary to detect *H. pylori*-resistant profiles of the gastric stump in order to preserve high eradication rates. The purpose of this study was to examine *H. pylori* infection rate and to evaluate the antibiotic susceptibility of *H. pylori* to metronidazole, clarithromycin, levofloxacin, amoxicillin, and furazolidone in gastric-remnant patients.

MATERIALS AND METHODS

Study Population

Patients who underwent gastroscopy in an urban hospital located in Zhejiang province of China between January 2009 and November 2017 and had a history of partial gastrectomy were retrospectively enrolled in the remnant stomach group. Inclusion criteria for gastric-remnant patients were as follows: more than 1 year after surgery; the surgical procedure was Billroth I, Billroth II, or Roux-en-Y reconstruction after partial gastrectomy, wedge resection, or proximal gastrectomy; and the surgical indication was peptic ulcer or gastric cancer. Contemporary non-gastrectomized patients were enrolled in the control group. Inclusion criteria were as follows: adults referred for gastroscopy for dyspepsia symptoms during the past 3 months and endoscopic diagnosis of chronic gastritis. Exclusion criteria for both groups included: previous eradication therapy and treatment with antibiotics, H2-receptor blockers, proton pump inhibitors, or bismuth salts within 1 month before endoscopy.

Gastric Mucosal Biopsy and Histology

Endoscopic biopsies were taken from the antrum and corpus of non-operated stomach, as well as lesser curvature and greater curvature of the gastric stump during gastroscopy. Tissue samples were routinely processed by formalin fixation and paraffin embedding. The presence of *H. pylori* and histopathological appearances of gastric mucosa were evaluated by hematoxylin and eosin stain.

H. pylori *Culture and Antibiotic Susceptibility Test*

The biopsy specimens preserved in the brain–heart infusion broth plus 5% glycerin were homogenized in individual microtubes and then the homogenates were plated onto Columbia agar with 5% sheep blood. All plates were incubated for 72 hours at 37°C under microaerophilic conditions (5% O_2, 10% CO_2, and 85% N_2). *H. pylori* was identified by gram staining, colony morphology, catalase, oxidase, and urease test. The identified strains were stored at −80°C for future analyses. Agar dilution method was applied to antibiotic susceptibility test, which was performed according to previous studies.[25] Three microliters of bacterial suspension with a turbidity of 0.5 McFarland standard were transferred onto the surface of Mueller–Hinton agar plates with 5% sheep blood and a single antibiotic. A plate without an antibiotic was simultaneously used as control. All plates were incubated at 37°C in a microaerophilic chamber for 72 hours. Antibiotic-resistant criteria were used as follows: MIC ≥ 8 μg/mL for metronidazole,[26,27] MIC ≥ 1 μg/mL for clarithromycin,[28] MIC ≥ 2 μg/mL for levofloxacin (29, 30), MIC ≥ 2 μg/mL for amoxicillin,[29,30] and MIC ≥ 2 μg/mL for furazolidone.[31,32] Figure 1 shows the growth of *H. pylori* with different metronidazole doses by the agar dilution method.

Statistical Analysis

Statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) program. Continuous data were reported as mean and standard deviation and were compared by the Student's *t*-test, while categorical data were reported as a percentage and were compared by chi-square test. The concordance between 2 testing methods was evaluated by Cohen's kappa coefficient.

RESULTS

The present study enrolled 728 gastrectomized patients and 5035 non-gastrectomized patients. There were no significant differences in age and gender between 2 groups. Among 728 gastrectomized patients, 63 (8.65%) were identified as *H. pylori* infection by bacterial culture. Of those, the surgical indications were gastric cancer in 44 patients (69.84%) and peptic ulcer in 19 patients (30.16%). Mean duration after surgery was 88.25 ± 79.63 months. Among 5035 non-gastrectomized patients, 17.76% of the subjects were infected with *H. pylori* (894 of 5035 patients). The *H. pylori* infection prevalence in

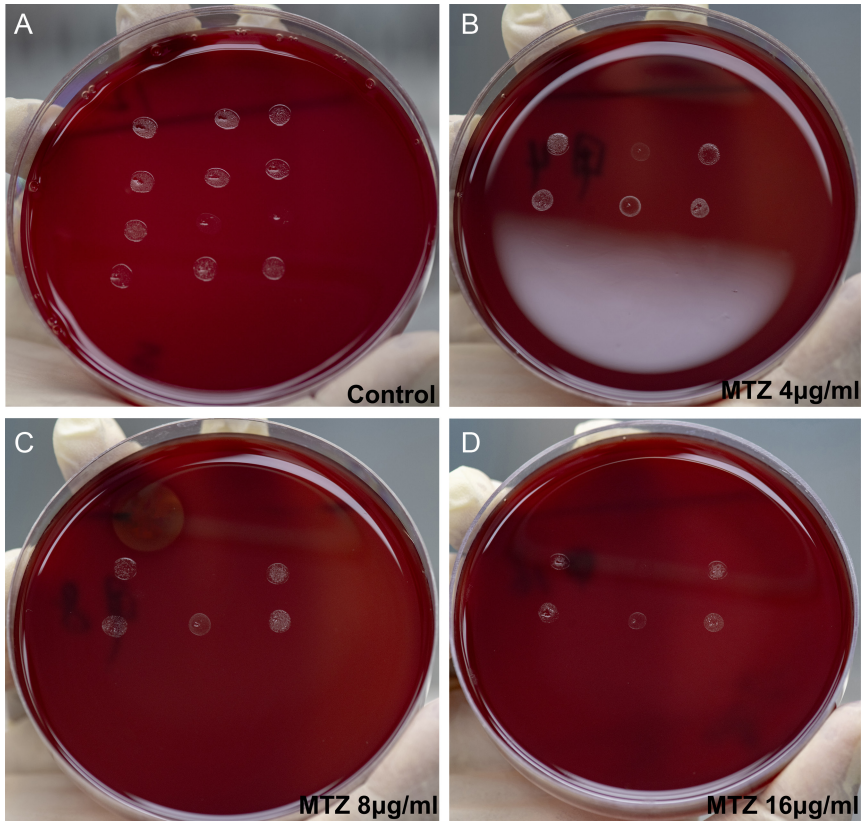

Figure 1. Determining the susceptibility of *Helicobacter pylori* to metronidazole by the agar dilution method. (A) Growth control (no antibiotics). The strains in the above 2 lines were inoculated immediately after the preparation of the bacterial suspension, and the following 2 lines of the same strains used for time control were inoculated 30 minutes after the preparation of the bacterial suspension. (B) Metronidazole at 4 mg/μL. (C) Metronidazole at 8 mg/μL. (D) Metronidazole at 16 mg/μL. MTZ, metronidazole.

the non-gastrectomized group was much lower than that in the general population,[4,25] which can be explained by the exclusion of patients with peptic ulcer or gastric cancer who have high rates of *H. pylori* infection. Meanwhile, 69 gastrectomized patients (9.48%) and 925 non-gastrectomized patients (18.37%) were confirmed *H. pylori*-positive by histologic examination. There was a good concordance (95.30%) between the bacterial culture and the histology (kappa scores of 0.833). *H. pylori* infection rate in the remnant stomach was significantly lower than that in the control group by 2 testing methods (both $P < .001$).

Among 63 isolates of *H. pylori* from gastrectomized patients, all isolates (100%) were resistant to metronidazole, 13 (20.63%) were resistant to clarithromycin, and 14 (22.22%) to levofloxacin. However, all strains were susceptible to amoxicillin and furazolidone. Among 894 isolates of *H. pylori* from non-gastrectomized patients, metronidazole resistance was detected in 809 isolates (90.49%), clarithromycin resistance in 220 isolates (24.61%), and levofloxacin resistance in 194 isolates (21.70%). Only a very small number of isolates were resistant to amoxicillin (0.22%) and furazolidone (0.11%). Gastric-remnant patients had a significantly higher metronidazole resistance rate than non-gastrectomized patients ($P = .005$). However, the resistance rates of clarithromycin, levofloxacin, amoxicillin, and furazolidone did not differ significantly between the 2 groups (Table 1).

An analysis of resistance rates in gastric-remnant patients with different clinical and demographic variables is presented in Table 2. Of the 63 gastrectomized patients, clarithromycin resistance in men was higher than that in women (25% vs. 0%, $P = .100$), but the difference was not statistically significant. We also did not observe a significant difference in levofloxacin resistance with respect to sex. Meanwhile, there were no significant differences between different age groups in the rates of resistance to clarithromycin and levofloxacin.

Table 1. Antibiotic Resistance of *Helicobacter pylori* in Gastrectomized Patients and Non-gastrectomized Patients

	Antibiotic-Resistant Rate (%)		
Antibiotic	Remnant Stomach Group (n = 63)	Control Group (n = 809)	*P**
Metronidazole	100	90.49	.005
Clarithromycin	20.63	24.61	.546
Levofloxacin	22.22	21.70	.876
Amoxicillin	0	0.22	1.000
Furazolidone	0	0.11	1.000

**P* value for remnant group versus control group.

When antibiotic resistance was compared between the peptic ulcer group and gastric cancer group according to surgical indication, it was observed that there was an increasing percentage of clarithromycin resistance in the gastric cancer group, although the increase was not statistically significant (gastric cancer group vs. peptic ulcer group: 27.27% vs. 5.26%, *P* = .086). Meanwhile, no significant change was detected between 2 groups in levofloxacin resistance.

DISCUSSION

H. pylori infection is commonly found in the gastric mucosa. With the postoperative changes of gastric environment, the susceptible sites for *H. pylori* infection might shift from the antrum to the proximal residual stomach (fundus and corpus of the stomach).[24] In some cases, the original infection of *H. pylori* may not be eliminated after gastrectomy; in other cases, the patients might be reinfected with *H. pylori* despite spontaneous elimination of *H. pylori* after gastrectomy. *H. pylori* infection rate in the gastric stump ranged from 21.5% to 65.1% across different countries,[12,24,33-39] and the infection rate in our study was as low as 8.65%. This discrepancy is possibly attributable to exclusion of patients who have previously been treated for *H. pylori* infection in the present study. In addition, our data show a significantly lower *H. pylori* infection rate in gastric-remnant patients than in non-gastrectomized patients. The change in postoperative *H. pylori* infection rate may be due to decreased survivability of *H. pylori* in the remnant stomach, as well as increasing reflux of alkaline digestive juices which seem to prevent *H. pylori* growth.[40] These various reports further highlight the necessity for the investigation on *H. pylori* status in the remnant stomach.

Whether gastrectomy has an effect on the development of drug-resistant strains is uncertain. Several studies reported that Roux-en-Y gastric bypass and sleeve gastrectomy could result in acute and sustained changes in the gut microbiome.[41-43] These altered bacteria could provide the resident human microflora with the chance to transfer or acquire drug-resistance determinants.[44] On the other hand, antibiotics for prophylaxis or treatment of postoperative infection might be associated with a change in the antimicrobial susceptibility profiles of pathogens. Overuse or misuse of antibiotics could cause an overgrowth of drug-resistant bacteria.[45] Moreover, non-resistant bacteria might become resistant through contact with the administered antibiotics.[46] However, data regarding *H. pylori* antimicrobial resistance in gastrectomized patients are lacking. To our knowledge, our study is the first retrospective study investigating resistance profiles of *H. pylori* in the remnant stomach. Metronidazole resistance was 100% in the gastric-remnant patients, which was significantly higher than that

Table 2. Factors Related to the Antibiotic Resistance of *Helicobacter pylori* in Gastric-Remnant Patients

	Resistance Rate (%)				
Characteristics	Metronidazole	Clarithromycin	Levofloxacin	Amoxicillin	Furazolidone
Sex					
Female (n = 11)	100	0	9.09	0	0
Male (n = 52)	100	25	25	0	0
Age(years)					
<65 (n = 39)	100	15.38	25.64	0	0
≥65 (n = 24)	100	29.17	16.67	0	0
Surgical indication					
Peptic ulcer (n = 19)	100	5.26	10.53	0	0
Gastric cancer (n = 44)	100	27.27	27.27	0	0

in the non-gastrectomized patients (90.49%). It was surprising to determine such a high prevalence of metronidazole resistance in the remnant stomach. In contrast with our study, rates of metronidazole resistance in non-gastrectomized patients from other countries and regions ranged from 30.7% to 67.9%.[17,19,20,26] The possible reasons for high metronidazole resistance are as follows: some gastric-remnant patients had gut microbial changes caused by gastrectomy.[41-43] The modifying activity or inactivation of metronidazole by facultative anaerobic organisms has been observed when facultative anaerobic bacteria were cultured together with metronidazole-sensitive bacteria.[47-49] Therefore, we speculate that the effect of metronidazole on *H. pylori* might be influenced by the presence of other bacteria following gastrectomy. So it can be seen that metronidazole is not recommended as a first-line empirical treatment for postoperative patients. The detected prevalence of both clarithromycin and levofloxacin resistance was over 20% in the present study, which was similar to the reports in non-gastrectomized patients from other countries and regions.[29,50,51] Possibly this is due to the widespread use of these drugs to treat nasopharyngeal tonsil infection and respiratory infection.[52-55] Furthermore, rare resistance to amoxicillin was observed in gastrectomized patients and non-gastrectomized patients in the present study. One possible reason is that *H. pylori* resistance to metronidazole, clarithromycin, and levofloxacin might be due to single-point mutation, whereas amoxicillin resistance is caused by multiple-site mutations.[56-59] However, a notable finding by Japanese researchers was that the bacteria in the remnant stomach could produce β-lactamase, and thus, *H. pylori* in the gastric-remnant patients might survive despite amoxicillin treatment.[44] This difference may be attributed to the frequent use of cephalosporin during perioperative period in Japan.[60] Likewise, resistance to furazolidone was very rare in gastrectomized patients and non-gastrectomized patients. The resistance rates of furazolidone remained low (less than 5%) over time in China.[25,29,61-63]

However, it is important to note some limitations of the present study. First, the number of *H. pylori*-positive postoperative patients was far below the expected sample size, which limited the power of this study. There is not enough sample size to compare *H. pylori* infection rates among different time periods and different surgical procedures. Likewise, it is possible that the number of samples is not sufficient to assess the relationship between resistance rates and clinical parameters. Second, the exact data regarding *H. pylori* status were not collected before and immediately after the operation. According to several reports, *H. pylori* might be spontaneously cleared after gastrectomy.[5,6] As mentioned above, some *H. pylori*-positive subjects may be infected with *H. pylori* before gastrectomy, and others might be reinfected with *H. pylori* after gastrectomy. Third, as a single-center retrospective study, there is an inherent risk of selection bias and information bias. A multicenter, large sample, and long follow-up study may solve these problems.

In conclusion, a significantly lower prevalence of *H. pylori* was found in the remnant stomach than in the non-operated stomach. *H. pylori* metronidazole resistance was as high as 100% in patients after partial gastrectomy, and the detected resistance rates to clarithromycin and levofloxacin were both over 20%. Gastric-remnant patients had a significantly higher metronidazole resistance rate than non-gastrectomized patients. Continuous surveillance of antimicrobial susceptibility in gastric-remnant patients is essential in order to achieve optimal therapy regimens and prevent treatment failures.

Ethics Committee Approval: The study was approved by the medical ethics committee of the First Affiliated Hospital of Zhejiang University (No: 2016-20).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Conflict of Interest: The authors have no conflict of interest to declare.

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