The Relationship between Previous Fluoroquinolone Use and Levofloxacin Resistance in *Helicobacter pylori* Infection

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The relationship between prior fluoroquinolone use and levofloxacin resistance in *Helicobacter pylori* infection is unknown. Among 125 enrolled patients, 8.8% had *H. pylori* isolates that were resistant to levofloxacin. Levofloxacin resistance was associated with any prior fluoroquinolone use over the previous 10 years and with the total number of fluoroquinolone courses prescribed (P<.001).

*Helicobacter pylori* is a common pathogen that infects ~40% of individuals in developed countries and >90% of individuals living in developing countries [1, 2]. *H. pylori* infection is known to cause gastritis, peptic ulcer disease, and mucosa-associated lymphoid tissue lymphoma, and it is the leading cause of gastric adenocarcinoma [3]. Annual rates of reinfection with this organism vary widely (<1% to >70%), with higher rates in developing countries, compared with developed countries; 14.5% of urban Alaska Native persons have been documented to be reinfected 2 years after successful treatment [4].

Treatment failure has been reported in 15%–20% of patients who are treated with antimicrobials [5]. In the United States, 10%–12% and 24%–28% of *H. pylori* isolates demonstrate antimicrobial resistance to clarithromycin and metronidazole, respectively [6, 7]. Resistance to these antimicrobials has led to the recent use of levofloxacin in combination with other antimicrobial agents plus a proton pump inhibitor to treat infection with *H. pylori* [8–12]. Levofloxacin is widely used alone or as empiric therapy for a variety of infections. Use of levofloxacin as a single agent is unlikely to eradicate infection with *H. pylori*; thus, incidental fluoroquinolone treatment could exert pressure on an existing *H. pylori* infection, selecting for fluoroquinolone-resistant strains.

At present, levofloxacin is infrequently used as a part of the standard multidrug regimen to treat primary *H. pylori* infection; however, multidrug regimens containing levofloxacin are coming into more common use as second-, third-, or fourth-line therapies, with eradication rates ranging from 63% to >90% [9–11, 13–17]. An earlier study in Alaska [18] demonstrated a strong association between previous use of macrolides or metronidazole and resistance of *H. pylori* to these antimicrobial agents. At the time of our previous study [18], quinolones were infrequently used as a treatment option for *H. pylori* infection, and antimicrobial susceptibility testing for levofloxacin was not being performed in our laboratory. However, recent data indicate that fluoroquinolones are a viable and effective second- or third-line treatment option for *H. pylori* infection. This shift in treatment options and the fact that fluoroquinolones are so widely used led us to determine whether there was an association between prior fluoroquinolone use and resistance of *H. pylori* to levofloxacin.

**Patient and data collection.** From September 1998 through June 2002, the Arctic Investigations Program of the US Centers for Disease Control and Prevention and the Alaska Native Medical Center (ANMC) conducted a study among Alaska Native people living in an urban setting (Anchorage, AK) to determine the reinfection rate following eradication of *H. pylori* infection. This study was approved by the institutional review boards of the Centers for Disease Control and Prevention and the Alaska Area Native Health Service. All patients who enrolled in the study provided written, informed consent for study participation.

Data collection methods for this study have been previously described [18]. In brief, from September 1998 through June 2002, all Alaska Native persons ≥18 years of age from the Anchorage area who were scheduled to undergo esophagogastroduodenoscopy were invited to participate. Patients who had a history of an immunodeficiency disorder or who were taking immunosuppressive therapy were excluded from the study. Patient care information was assessed via electronic medical records at ANMC in which all outpatient health care visits and outpatient pharmacy encounters have been recorded since 27 September 1990. Records were searched for all antimicrobial...
prescriptions filled by study participants for the 10 years prior to diagnosis of H. pylori infection. Participants who had <8 years of records available for review were excluded from the data analysis. Emergency room and inpatient hospital antimicrobial therapy received by study participants was also recorded during the same time period.

**Biopsy and culture.** All patients recruited for the study had 1–3 gastric biopsy specimens retrieved for culture, antimicrobial susceptibility testing, and histological examination. Tissue culture and H. pylori identification were performed using standardized microbiologic practices [18]. For each individual H. pylori culture, susceptibility to levofloxacin was determined using a gradient diffusion method (Etest; AB Biodisk). H. pylori isolates were defined as levofloxacin resistant if the MIC was \( \geq 2 \) \( \mu \)g/mL for levofloxacin. Among participants in whom multiple H. pylori isolates were found, the isolate with the highest MIC determined from all of the cultures was used for analysis.

**Statistical analysis.** Univariate ORs, risk ratios, and the \( \chi^2 \) test for trend were calculated using Epilinfo, version 6.04b (Centers for Disease Control and Prevention). \( P \) values were 2-tailed, and values <.05 were considered to be statistically significant.

**Patient profiles.** One hundred twenty-five Alaska Native persons with culture-confirmed H. pylori infection who had medical records at ANMC dating back at least 8 years prior to diagnosis participated in the study. The median age of participants was 46.5 years (range, 22.2–88.7 years), and 82 participants (65.6%) were female. Pharmacy records for each patient were available for a median of 8.6 years (range, 8.0–9.6 years) with a median of 11 total antimicrobial courses being prescribed to all participants (range, 0–68 courses). None of the 125 patients were related to each other or shared a household. Twenty-eight patients had been prescribed a fluoroquinolone antibiotic during the 8–10 years prior to enrollment; the median number of courses prescribed was 1.

**Levofloxacin resistance and fluoroquinolone use.** Persons with levofloxacin-resistant H. pylori isolates and persons with levofloxacin-susceptible isolates were similar with respect to sex and number of years of available medical records, but there was a statistically significant difference in age; persons with levofloxacin-resistant isolates were older (mean age, 56 years vs. 47 years; \( P = .02 \)). Among the 125 participants, 11 (8.8%) were found to have H. pylori isolates that were resistant to levofloxacin; 9 had an MIC of 32 \( \mu \)g/mL, 1 had an MIC of 8 \( \mu \)g/mL, and 1 had an MIC of 4 \( \mu \)g/mL (figure 1). Among these 11 patients with levofloxacin-resistant isolates, 9 (82%) had been prescribed a fluoroquinolone in the 10 years prior to diagnosis, compared with 19 (17%) of 114 patients who had levofloxacin-susceptible isolates (\( P < .001 \)). Of the 28 persons in this cohort who had been prescribed a fluoroquinolone, 9 (32%) were found subsequently to have a levofloxacin-resistant infection, compared with only 2 of the 97 persons with no known use of a fluoroquinolone (risk ratio for a resistant infection, 15.6; \( P < .001 \)). The percentage of levofloxacin-resistant isolates increased with an increasing number of previous courses of levofloxacin received (table 1).

**Discussion.** We found that 8.8% of Alaska Native adults in this study were infected with an H. pylori isolate that was resistant to levofloxacin. We demonstrated a strong correlation between a patient’s previous use of fluoroquinolones and subsequent isolation of levofloxacin-resistant H. pylori, as well as a dose-response relationship between the risk of infection with a resistant isolate and increasing number of fluoroquinolone
To our knowledge, this is the first study that links previous fluoroquinolone use to levofloxacin resistance in persons infected with *H. pylori*.

At present, levofloxacin is rarely used as part of the standard multidrug regimen to treat primary *H. pylori* infection; however, multidrug regimens using levofloxacin are coming into more common use in patients for whom previous treatment(s) have failed, with eradication rates ranging from 63% to >90% [9–11, 13–16]. Treatment success depends, in part, on patient compliance, but also on the proportion of *H. pylori* isolates that demonstrate fluoroquinolone resistance (which is caused by point mutations in the gyrA/B gene). Data from this study demonstrate the incidence of levofloxacin resistance to be relatively low (<10%) among isolates from Alaska Native persons; however, antibiotic prescription rates in this cohort are higher than those reported in the United States in general (1.52 courses vs. 0.44 courses per person per year, respectively) [19] and the number of fluoroquinolone prescriptions (levofloxacin and ciprofloxacin combined) at ANMC from 1998–2004 has increased 3-fold, indicating that fluoroquinolone-resistance rates could increase in the future.

The proportion of isolates demonstrating resistance to levofloxacin varies geographically and it is likely related to fluoroquinolone consumption by country or region. Recent studies from France, Germany, Portugal, and Canada report that <10% of *H. pylori* isolates have levofloxacin resistance [20–23]; however, other recent studies demonstrate levofloxacin resistance ranging from 17% of isolates in Jamaica to 21.5% and 31% in Korea and Italy, respectively [14, 24, 25]. Data from these studies demonstrate considerable geographic variability in fluoroquinolone-resistance rates and argue for a regional or community-based approach to surveillance to monitor emerging resistance of *H. pylori* isolates to fluoroquinolones and other classes of antimicrobial agents.

There are several limitations to consider. This is not a population-based study; patients undergoing endoscopy for gastrointestinal complaints were sequentially enrolled, which may, therefore, limit the generalizability of our results. We collected data from medical providers at only 1 institution. In addition, we were unable to evaluate distant use of antibiotics in relation to resistance, because we only collected antibiotic prescription data beginning in 1990, whereas fluoroquinolone use began in the mid 1980s. We acknowledge the potential for incomplete capture of antibiotic use in this study; however, our record review likely captured most antibiotic use by participants during the study period, because health care and prescriptions are provided for Alaska Native people through obligations by the federal government. Lastly, the Clinical and Laboratory Standards Institute has not yet designated MIC breakpoints of fluoroquinolone resistance for *H. pylori* isolates; therefore, we chose the breakpoint of 2.0 μg/mL for levofloxacin, according to published reports that support using breakpoints from 1.0 to 8.0 μg/mL [9, 10, 14, 20–22, 26].

Several important clinical points can be made from this study. When considering a second-line therapy regimen for patients for whom their first course of therapy failed, patient-specific data on antimicrobial susceptibility could be useful to the practitioner in guiding the choice of antibiotic agents; unfortunately, susceptibility data are rarely available. When a second or third course of therapy is being considered for patients who have experienced failure of their first course, a detailed history of past fluoroquinolone (and macrolide) use should be sought, and if found, the possibility of resistance should be considered when prescribing therapy. This study also highlights the importance of appropriate use of levofloxacin to limit the development of antimicrobial resistance. In regions where drug-resistant *H. pylori* infection is common and treatment-failure rates are high, providers should strongly consider performing a posttreatment test for cure to confirm the successful eradication of this organism.

### Acknowledgments

**Financial support.** Centers for Disease Control and Prevention.

**Potential conflicts of interest.** All authors: no conflicts.

### References


### Table 1. Relationship between infection with levofloxacin-resistant *Helicobacter pylori* and the total number of courses of fluoroquinolone antibiotics prescribed before diagnosis among 125 Alaska Native persons, 1998–2002.

<table>
<thead>
<tr>
<th>No. of courses of fluoroquinolone</th>
<th>Patients with levofloxacin-resistant <em>H. pylori</em> infection, % (proportion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2 (2/97)</td>
</tr>
<tr>
<td>1</td>
<td>17 (3/18)</td>
</tr>
<tr>
<td>2</td>
<td>25 (1/4)</td>
</tr>
<tr>
<td>3</td>
<td>50 (1/2)</td>
</tr>
<tr>
<td>4</td>
<td>100 (1/1)</td>
</tr>
<tr>
<td>5</td>
<td>100 (3/3)</td>
</tr>
</tbody>
</table>

**Note.** *P* < .001 by logistic regression.