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EDITORIAL

Helicobacter pylori Gastritis: Susceptible to Further Testing?

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Background and Significance

Antibiotic resistance has reached crisis proportions in the USA. A report from the Antibiotic Resistance Working Group of The President's Council of Advisors on Science and Technology [1] states that the "Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) each recently identified antibiotic resistance as one of the greatest threats to human health worldwide. CDC estimates that each year more than two million people in the United States are sickened with infections by more than 17 types of antibiotic-resistant microbes." Interestingly, of the 18 organisms specifically cited in the report, none was *H. pylori*.

The prevalence of *H. pylori* in the general US population is unknown; in 1999–2000, 25.4 % of the US population was seropositive [2]. Other studies described a prevalence rate of 30–40 % in US adults and a 60–70 % infection rates in immigrant populations and those of lower socioeconomic status and living under crowded circumstances [3, 4]. Resistance to clarithromycin, one of the components of recommended first-line therapy, has been increasing, with 10–15 % resistance in 2004 [5] and ~30 % resistance reported in the article by Park et al. [6] in this issue of *Digestive Diseases and Sciences*. Given that 320,000,000 people live in the USA, the number of persons infected with clarithromycin-resistant *H. pylori* is estimated in the hundreds of thousands, similar or greater than the estimated annual infections by carbapenem-resistant or β-lactamase-producing Enterobacteriaceae (35,300), drug-resistant Campylobacter (310,000), or vancomycin-resistant Enterococcus (20,000) [1].

As with the prevalence rates of *H. pylori* infection, resistance rates, a major factor in determining the success of eradication therapy, also vary worldwide depending on geographic regions. In many countries, the primary antimicrobial resistance to clarithromycin has increased to levels above the recommended threshold for use as a first-line agent for *H. pylori* infection. In a recent nationwide population-based Korean study, the antibiotic resistance rates of *H. pylori* were distinct in different regions. The authors strongly recommended that local data should be provided as a guideline for treating *H. pylori* infection. In a Vietnamese study, clarithromycin resistance, which exceeded 50 % in young children, was a significant cause of treatment failure. The authors suggested that clarithromycin should not be used as part of *H. pylori* eradication therapy in children if their antibiotic susceptibility profile is unknown [7–10]. The conclusions of the authors from these aforementioned studies reflect a distinct change in the approach to management of *H. pylori* infection, which is targeted therapy based on resistance profiles, rather than the disease outcomes. Furthermore, and closer to home, a recent review from Latin America described high rates of resistance of *H. pylori* to first-line antibiotics; the authors recommended susceptibility testing prior to the use of clarithromycin [11]. Therefore, treatment failure, primarily due to increasing resistance rates, raises the cost of *H. pylori* infection management and the burden of this infection and associated disease to the patient and their

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family. The inability to initially eradicate *H. pylori* infection will increase healthcare utilization, increasing the number of unnecessary procedures and therapies and their associated risks. Moreover, eradication failure increases the risk of antibiotic resistance of the infecting *H. pylori* strains, thereby reducing the likelihood of successful eradication.

Helicobacter pylori is not only an infectious organism, but also an oncogenic agent. The WHO has classified *H. pylori* as a class 1 carcinogen based on data that support the contention that this organism meets all of Koch's postulates as a human gastric carcinogen. With a near threefold increase in gastric carcinoma among patients who are seropositive for *H. pylori*, eradication of the infection decreases the incidence of cancer development [12]. In "at-risk" *H. pylori*-infected populations, without an effective vaccine, there is a need to treat with appropriate, highly effective and targeted therapy to eradicate the organism in infected individuals.

How the Article Addresses the Controversies

One clear message highlighted by Park et al. [6] is that the current rate of clarithromycin resistance for *H. pylori* in the USA exceeds the rate at which empiric therapy is recommended, yet empiric therapy is the standard treatment for *H. pylori* gastritis. The authors report a >20 % rate of clarithromycin-resistant *H. pylori* gastric infection, identified through genetic sequencing of *H. pylori* DNA extracted from paraffin-embedded tissue sections submitted from four locations across the USA. The prevalence of clarithromycin resistance varied from 23.1 to 45.8 %; the only factor impacting the resistance rate was a history of prior treatment failure. There have been numerous reports of similar or higher resistance rates to clarithromycin throughout the world and in specific locations in the USA, but this is the first article to assess prevalence in multiple locations, therefore identifying clarithromycin-resistant *H. pylori* as an important public health problem. Thus, the conceptual approach to management of *H. pylori* infection-associated disease by gastroenterologists, which has been to resolve the disease outcome, must change to one that addresses the infection as an infectious disease.

To expand on the discussion in the article, the 2007 management guideline for *H. pylori* infections from the American College of Gastroenterology notes that the efficacy of first-line treatment with a proton pump inhibitor (PPI), clarithromycin, and amoxicillin has decreased to 70–85 %, in part due to clarithromycin resistance [13]. The 2007 article states that poor compliance and antibiotic resistance are the most important predictors of treatment failure, citing articles published in 2002 [14] and 2004 [5] describing >20 % resistance for metronidazole, <2 % resistance for amoxicillin, and 10–13 % resistance for clarithromycin.

Park et al. advise that "antibiotic resistance testing, in particular for clarithromycin resistance, of individuals diagnosed with *H. pylori* infection should be performed to help tailor antibiotic therapy to a regimen with a high likelihood of success." This recommendation then reflects a change in management strategy—from one designed to resolve disease—to one that is designed more appropriately to treat the infection. Antibiotic resistance of *H. pylori* strains, though, is not limited to clarithromycin. The following rates of *H. pylori* resistance were reported in a 2015 report from Shanghai, China: clarithromycin 40.0 %, amoxicillin 4.4 %, metronidazole 53.3 %, tetracycline 0 %, and levofloxacin 55.6 % [15]. While testing for clarithromycin resistance alone will provide important information, to treat *H. pylori* gastritis as an infectious disease will require available testing for not only clarithromycin, but also for other commonly used antibiotics. Studies are beginning to appear that demonstrate more acceptable eradication rates when therapy is tailored according to the antimicrobial susceptibility profile, rather than the traditional empiric therapy that has been used for the past 25 years [16]. Despite the knowledge of resistance, there was, counterintuitively, no strong recommendation made by the American College of Gastroenterology for antibiotic resistance testing to be performed prior to prescribing antibiotics [13]. The lack of readily available antibiotic susceptibility testing methods makes treating *H. pylori* like an infectious disease difficult. Culture of *H. pylori* requires a strict microaerophilic environment with 5 % CO_2 at 35 °C for 3–7 days, complicating identification and antibiotic resistance testing [17]. With many clinical laboratories unable to grow the organism and perform the current FDA-recommended method for antimicrobial resistance testing, namely agar dilution, targeted eradication strategies for *H. pylori*-infected persons have not been undertaken as part of a routine treatment plan.

Several molecular assays have been developed to identify the bacterial genetic alterations conferring resistance for the antibiotics used to treat *H. pylori*, providing similar susceptibility profiles when compared to culture-based methodology [18–21]. While some of the molecular assays are in clinical use, such as the assay used by Park et al., the methods are not used in most clinical laboratories because of the complexity of the assays. Furthermore, to test all of the antibiotics used to treat *H. pylori* for resistance would require assays for multiple gene targets and, therefore, additional complexity.

Summary and Future Directions

It is time to treat *H. pylori* infections with therapy that is appropriate, using precision medicine to match antibiotic therapy with the resistance pattern. To do this will require readily available diagnostic testing for the confirmation of infection, and the ability to perform timely antibiotic resistance testing. Empiric treatment, no longer appropriate in many areas due to the high level of antibiotic resistance, must be supplanted by antibiotic resistance testing or by alternative first-line therapy. Soon-to-be published guidelines for the management of *H. pylori* infection in children will specifically recommend pre-treatment susceptibility profiles, a knowledge (if available) of prevalence trends for *H. pylori* strains from within the region, and targeted, highly effective eradication therapy (i.e., eradication rates >90 %). Furthermore, due to the unacceptably low *H. pylori* eradication rates in children and adults reported in the literature from different countries, as well as the increasing rates of antibiotic resistance among all subjects of all ages, treatment for *H. pylori* in children as well as adults should be provided when it is clinically indicated, and with the most effective therapy available—one which is based on the susceptibility profiles of the infecting strain. Until the time when the technology evolves to the point that antibiotic resistance testing for this organism is routine for all clinical laboratories, local prevalence should be determined and, if this exceeds 20 %, susceptibility testing for clarithromycin, at the least, should be requested from those laboratories that are able to perform the assay. Laboratories should work diligently to develop methodologies (a "gold standard") that employ molecular tools to enable rapid, efficient, highly robust testing of infecting *H. pylori* strains to then offer effective, targeted eradication therapy.

Future studies should focus on obtaining antibiotic resistance rates across regions to help direct optimal therapy, and monitor trends in resistance. Furthermore, high-quality studies evaluating novel approaches and therapies including concomitant therapy and the contribution of supplemental probiotics are needed. Importantly, studies of prevention of infection with optimization of vaccine strategies should be performed such that the use of antibiotics for *H. pylori* infection can be curtailed, particularly in highly prevalent areas that also have substantial disease burdens from this chronic human infection.

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