Helicobacter pylori and Gastric Cancer: Detection of Clarithromycin Resistance and Molecular Approaches

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HIGHLIGHTS

- *Helicobacter pylori* (*H. pylori*) is the strongest environmental risk factor for gastric adenocarcinoma and was classified by the IARC in 1994 as a Group 1 carcinogen.
- Approximately 75% of global gastric cancer cases are associated with *H. pylori* infection; infection increases the risk of gastric cancer by 3–6 times.
- An estimated 4.4 billion people worldwide are infected with *H. pylori*.
- Globally, clarithromycin resistance has exceeded 20–50%, and the success rate of classical triple therapies has fallen below 60% in most regions.
- The wider adoption of molecular diagnostics and resistance/genetics-based strategies contributes to treatment success and to reducing the incidence of gastric cancer.

INTRODUCTION

H. pylori is among the most common chronic bacterial infections worldwide, affecting ~4.4 billion people, with prevalence exceeding 70% particularly in low- and middle-income countries (Hooi et al., 2017). It is classified by the WHO and IARC as a Group 1 carcinogen and is one of the most important preventable causes of gastric cancer (IARC, 1994; Sung et al., 2021). Prevalence is 70.1% in Africa and 69.4% in Latin America, compared with 37.1% in North America and 24.4% in Oceania (Hooi et al., 2017). In a multicenter study in Türkiye, prevalence was 82.5%, contributing substantially to the high morbidity-mortality burden of gastric cancer (Özaydın et al., 2013). Mortality is driven less by the infection per se than by complications such as gastric adenocarcinoma and peptic ulcer disease; gastric cancer causes ~770,000 deaths annually and ranks fifth among cancer deaths, showing a strong correlation with the high infection burden in the Asia-Pacific region (Sung et al., 2021). Rising antibiotic resistance underscores the importance of innovative molecular approaches in diagnosis and therapy.

The spiral-shaped, Gram-negative, microaerophilic *H. pylori* moves through the gastric mucus via flagella; through urease, it hydrolyzes urea to ammonia and CO_2, thereby increasing local pH; via its LPS and adhesins such as BabA/SabA it adheres to the epithelium and manipulates host immunity to sustain chronic inflammation (Kusters et al., 2006; Backert & Clyne, 2011; Doohan et al., 2021). The toxins CagA and VacA disrupt cellular signaling pathways, contributing to tissue damage and carcinogenesis (Hatakeyama, 2014). Cultured and identified by Marshall and Warren, this bacterium overturned the paradigm that gastric acid prevents colonization; infection can establish a dynamic equilibrium with the host over many years and clinically ranges from asymptomatic carriage to severe disease (Marshall & Warren, 1984).

Clinical Outcomes of *H. pylori* and Its Relationship with Cancer

Although often asymptomatic, *H. pylori* drives a broad clinical spectrum through sustained host interaction: histopathological chronic active gastritis is observed in nearly all cases (Kusters et al., 2006); peptic ulcer disease develops in 10–20% of cases (Suerbaum & Michetti, 2002); and functional dyspepsia is reported in ~15–20% of infected individuals (Malfertheiner et al., 2017). In the rarer but critical outcome of MALT lymphoma, more than 90% of *H. pylori*–positive cases respond to eradication therapy, underscoring the bacterium's pivotal role in pathogenesis (Salar, 2019).

H. pylori is the strongest environmental risk factor for gastric adenocarcinoma and is classified by the IARC as a Group 1 carcinogen (IARC, 1994). Infection increases gastric cancer risk 3–6-fold; risk is more pronounced with CagA-positive strains, particularly for the intestinal type (Hatakeyama, 2014). Globally, ~75% of gastric cancer cases are attributable to *H. pylori* (Plummer et al., 2015). In 2020, with 1.1 million new cases and over 770,000 deaths, gastric cancer ranked fifth in incidence and fourth in mortality; there is a strong correlation between high *H. pylori* prevalence and cancer incidence in the Asia-Pacific region (Sung et al., 2021). Taken together, these data indicate that—given the spectrum from gastritis to ulcer disease and MALT lymphoma, and ultimately to a preventable cancer burden—diagnostic-therapeutic and eradication strategies should be a public health priority.

Treatment and Therapeutic Challenges

For many years, 14-day triple therapy with a proton-pump inhibitor (PPI) plus clarithromycin and amoxicillin/metronidazole was the standard; however, rising clarithromycin resistance has markedly reduced efficacy: in the presence of resistance, eradication typically falls below 60%, whereas in susceptible cases it exceeds 80–85% (Malfertheiner et al., 2017; Savoldi et al., 2018; Chey et al., 2024). Meta-analyses report mean global clarithromycin resistance of 22–28%, higher in Europe, the Eastern Mediterranean, and the Western Pacific, and in Türkiye ranging from 20–40% (Malfertheiner et al., 2017; Savoldi et al., 2018; Chey et al., 2024). The escalation of resistance, amplified by failed treatments, facilitates the spread of resistant strains, creating a public health problem that extends beyond individual patient management.

Detection of *H. pylori*

For *H. pylori* detection, histology, rapid urease testing, the urea breath test, and stool antigen assays generally yield sensitivity of 85–95% and specificity of 87–95%. Culture offers 100% specificity and the critical advantage of enabling antibiotic susceptibility testing; however, because it requires viable bacteria, sensitivity varies between 60–90% and the turnaround time is longer. Real-time PCR (qPCR) provides rapid results from both biopsy and stool specimens, is relatively less affected by transport and storage conditions, and can detect low bacterial loads. Although qPCR does not provide a phenotypic antibiotic susceptibility profile, it can directly identify resistance determinants—particularly *23S rRNA* mutations that confer clarithromycin resistance—thus delivering prompt and reliable information on resistance. Studies report qPCR sensitivity of 95–100% and specificity of 95–100%, with sensitivity of 97–100% and specificity of 93–98% for determining clarithromycin resistance (Pittie et al., 2024).

Clinically, qPCR is especially advantageous when conventional tests are negative but clinical suspicion persists, and when resistance status must be rapidly determined prior to antibiotic therapy (Pittie et al., 2024). Its applicability to stool samples offers a non-invasive and reliable alternative for patients in whom endoscopy is not feasible or preferred (Kusters et al., 2006). In sum, qPCR stands out in *H. pylori* detection for its speed and high sensitivity/specificity, whereas culture remains an indispensable reference for phenotypic susceptibility testing. Accordingly, the two methods are complementary in diagnostic and therapeutic decision-making (Chey et al., 2024).

CONCLUSION

H. pylori infection is a critical public health issue due to its high global prevalence and significant morbidity, particularly the development of serious complications such as gastric cancer and peptic ulcer disease (Hooi et al., 2017; Sung et al., 2021). Rising antibiotic resistance limits the effectiveness of standard treatment protocols and increases the risk of disseminating resistant strains following treatment failure (Malfertheiner et al., 2017; Savoldi et al., 2018). This situation directly affects not only individual patient outcomes but also the economic burden on national health systems and the global load

of gastric cancer (Sung et al., 2021). Broadening the use of molecular diagnostic methods—by enabling rapid and accurate detection of resistance genes—makes a substantial contribution to treatment success (Malfertheiner et al., 2017).

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