Managing *Helicobacter pylori*: elimination challenges

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Helicobacter pylori is a microaerophilic, spiral microorganism that colonizes and propagates lifelong in the human gastric microniches, if not treated. Its persistence is associated with a considerable risk of gastroduodenal disorders, including peptic ulcer diseases, gastric cancer, and mucosa-associated lymphoid tissue lymphoma.[1] Several regimens with different cure rates are used to treat this infection[2]; however, a monotherapy regimen with 100% clinical cure rate does not exist. A combination of two, three, or four antibiotics with a proton pump inhibitor is used generally as an empirical treatment,[3] with clarithromycin being the core antibiotic.[4] The escalating prevalence of *H. pylori* resistance to clarithromycin, however, has notably compromised the efficacy of these regimens. Meanwhile, the rationale and necessity for treating the infection in individuals with gastroduodenal symptoms have been debated.[5] *H. pylori* has been suspected to modify microRNAs and cause hypermethylation and double-stranded breaks in host DNA which can persist even after its elimination.[6] Altogether, the complex nature of such interactions may underlie the pathogenesis of gastric cancer though the exact mechanisms are unclear. Nevertheless, elimination to alleviate symptoms has primarily been recommended in the medical literature.[7]

Semantically, "eradication" and "elimination" may connote the same concept. However, clinically, "eradication" and "elimination"[8] of an infectious disease differ as defined by the Dahlem Workshop in 1997[9,10] but have seemingly been misused or gravely confused in the English context of *H. pylori*.[11–13] Elimination of the infection in individual cases, which involves the current treatment regimens,[12] should achieve complete removal of *H. pylori* confirmed by specific diagnostics at least four weeks after the completion of therapy.[14] Thus, elimination ideally removes the bacterial burden and potentially alleviates the symptoms. However, elimination may still coincide with the presence of the genetic material representing *H. pylori* strains in the biopsy samples of gastric antrum or corpus taken from asymptomatic patients.

Many clinical studies over the last 35 years have highlighted the benefits of *H. pylori* elimination in patients with newly confirmed or early-stage gastric cancer. However, a confirmatory direct causation has not been established.[15,16] Indeed, *H. pylori* elimination was found to reduce the incidence of gastric cancer in many regions worldwide. Contrarily, clinicians insist that treating *H. pylori* reduces only the risk of gastric cancer. Therefore, the *H. pylori* literature is still confused as to whether immediate elimination of *H. pylori* should ultimately be the goal. The high prevalence of undetected *H. pylori* infections in regions characterized by inadequate sanitation and overcrowded living conditions significantly contributes to intrafamilial transmission clusters and the development of antibiotic resistance. Particularly, asymptomatic carriers in resource-limited settings frequently remain undetected and untreated, thereby sustaining transmission cycles. Moreover, empirical therapies in these areas increasingly fail owing to rising resistance to clarithromycin, compounded by clonal dissemination of resistant strains. Thus, active case-finding through screening programs in communities, combined with susceptibility-guided regimens—for example, bismuth quadruple therapy in areas with high

resistance—may reduce reinfection rates. However, scaling up these strategies requires cost-effective diagnostics (e.g., stool antigen testing) and cross-sectoral partnerships to redress infrastructural barriers. Therapeutic regimens based on susceptibility testing can help determine the best available antibiotics against an active infection. Because *H. pylori* persists lifelong, a feasible approach to case-finding and immediate treatment may be useful to efficiently prevent the clinical sequelae in positive cases.[17] Indeed, *H. pylori* is prevalent in approximately half of the world's population.[18] Insufficient sanitation, low food hygiene, and poor or overcrowded living conditions are conducive to an elevated prevalence of *H. pylori* infection among institutionalized youth or adults and intrafamilial infection clustering.[19] Consequently, individuals with close contact with patients positive for *H. pylori*, assumingly all family members, should also receive effective treatment until microbiological or genetic testing confirms negative results. Such prevalence may be facilitated also by the clustered transmission of the antibiotic-resistant strains, which will require eliminating treatment. Therefore, in regions where considerably large populations are at high risk for gastric cancer, mass screening and elimination are practically and logically recommended. *H. pylori* culture and next-generation sequencing to test its susceptibility to antibiotics is not widely available, even with insurance coverage in the United States.[4] Also, next-generation sequencing has limitations primarily because it depends on the availability of gastric biopsies or stool samples. While this method is more advantageous than traditional microbiological testing, its widespread implementation, even in the United States, may be hindered by a lack of infrastructure and by the need for specific sample types. Future research should prioritize elucidating the molecular mechanisms underpinning host interactions with *H. pylori*, particularly emphasizing the modulation of host cellular pathways by bacterial virulence factors (e.g., *CagA, dupA*, and *vacA*) during carcinogenesis. Large-scale, population-level epidemiological studies are essential to evaluate the cost-effectiveness of mass-screening programs in high-prevalence regions and identify sociodemographic barriers to the implementation of prevention. Furthermore, translational studies into rapid, affordable antimicrobial susceptibility testing (e.g., CRISPR-based diagnostics) could redress challenges associated with antibiotic resistance. These multidisciplinary efforts will fill the gaps in understanding of *H. pylori* pathogenesis and inform targeted elimination strategies. While we unreservedly support the elimination programs against *H. pylori*, we would like to emphasize the clinical relevance of implementing the regimens rationally, contextual to specific individuals, families, clusters, communities, or geographical regions, and considering the complex interplay between the bacterium and the host. These considerations should be based on available resources, clinical and laboratory expertise, and the prevalence of resistance to antibiotics such as clarithromycin or amoxicillin. Eradication, which is a complete riddance of the infection globally, may be difficult to achieve because of complex factors.[20] Thus, directed management of *H. pylori* infections requires a balanced approach with targeted elimination strategies to redress the growing concern of antibiotic resistance.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Farid Rahimi: Conceptualization; Data curation; Validation; Writing – original draft; Writing – review & editing.

Amin Talebi Bezmin Abadi: Conceptualization; Data curation; Project administration; Validation; Writing – original draft; Writing – review & editing.

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