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Managing *Helicobacter pylori* infection: transitioning from conventional to alternative treatment approaches

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ABSTRACT

Helicobacter pylori, an essential constituent of the gastric microbiome in those infected, is commonly associated with medical conditions such as chronic gastritis, peptic ulcer disease, and gastric cancer. In recent years, the growing resistance to antibiotics worldwide has emerged as a substantial hurdle in the effective treatment of *H. pylori* infection. Consequently, it has necessitated the exploration of innovative treatment strategies aimed at bolstering the potency of existing antibiotic-based eradication therapies. Such avant-garde strategies include the incorporation of probiotics and prebiotics as complementary measures to *H. pylori* treatment, the use of antimicrobial peptides as potential replacements for traditional antibiotics, and the application of photodynamic therapy via ingestible devices. Other advanced methodologies entail deploying drug delivery systems that utilize microparticles and nanoparticles, the invention of vaccines, the exploration of natural products, and the potential use of phage therapy. This review offers a contemporary synopsis of these burgeoning strategies designed to suppress *H. pylori*, delving into their strengths, hurdles, and aspects to consider during their development. A significant achievement would be the creation of an efficient human vaccine; however, previous attempts at developing such vaccines have met with obstacles or even cessation. Numerous natural products have displayed anti-*H. pylori* properties, predominantly in laboratory environments. Nonetheless, a requirement remains for more extensive clinical studies to fully comprehend their role in exterminating *H. pylori*. Finally, phage therapy, while demonstrating potential as a suitable alternative, grapples with considerable challenges, chiefly the isolation of highly virulent bacteriophages that specifically target *H. pylori*.

Keywords: *Helicobacter pylori*, antibiotic resistance, innovative treatment strategies

Helicobacter pylori (H. pylori), a Gram-negative, helical bacterium, exhibits high global prevalence, infecting over half of the worldwide population [1, 2]. It primarily colonizes the gastric mucosa, constituting the majority of the gastric microbiota in those infected [3-7]. Infections with *H. pylori*, which typically initiates in childhood and can persist lifelong if left untreated, are linked to an array of gastric and extragastric conditions. These include chronic gastritis, peptic ulcer disease, gastric carcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma [8]. The pathogenic potential of individual *H. pylori* strains significantly influences these clinical outcomes, with certain virulence factors associated with an elevated risk of disease development [9-11].

H. pylori infection also impinges upon the gastric and gut microbiota, potentially playing a contributory

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role in both gastric and extragastric manifestations [12]. Nevertheless, the attempt to eradicate *H. pylori* via antibiotic therapy elicits concerns regarding the emergence of antibiotic-resistant strains and disruptions in the composition of the intestinal microbiota [13-17].

Owing to the high prevalence of *H. pylori* infection and its concomitant diseases, efficient eradication therapy is vital for clinical management. Contemporary treatment guidelines take into account previous antibiotic exposure and regional resistance rates to select the apt regimen. Triple therapy involving a proton-pump inhibitor (PPI), amoxicillin, and clarithromycin for a 14-day period is recommended as the first-line therapy in regions with low clarithromycin resistance [18]. An alternative option is Bismuth-containing quadruple therapy (BQT). In cases of high clarithromycin resistance, quadruple concomitant therapy or BQT is suggested [19]. Levofloxacin-based therapy is discouraged as a first-line treatment due to the escalating fluoroquinolone resistance [20]. Other recommended options include sequential therapy and fluoroquinolone-based LOAD therapy [21, 22]. The selection of the PPI molecule is also of importance, with second-generation PPIs demonstrating higher efficacy than their first-generation counterparts [23]. BQT is considered the most effective first-line therapy, while dual therapy employing amoxicillin and vonoprazan exhibits potential in East Asia [18, 24, 25].

Antibiotic resistance poses a major obstacle in *H. pylori* treatment, with eradication rates dwindling and resistance rates surging globally [25-29]. The improvement of diagnostic tools, such as non-invasive testing methods, is instrumental in combating antibiotic resistance [18, 30]. Additionally, factors related to patient compliance, side effects, and host genetic variants necessitate the exploration of alternative therapeutic approaches for *H. pylori* treatment.

Alternative Approaches for *H. pylori* Treatment

Innovative therapies for *H. pylori* infections strive to meet WHO standards for eradication rates, patient compliance, and prevention of antimicrobial resistance. These include strategies like the use of probiotics and prebiotics, antimicrobial peptides, photodynamic therapy, natural products, vaccines, micro- and nanoparticles, and phage therapy [31-34].

Probiotics are live microorganisms that confer health benefits. They modulate the immune response, generate antimicrobial substances, and compete with *H. pylori* for adhesion sites. Lactobacillus and Bifidobacterium are the commonly used probiotic genera [31, 35, 36]. Prebiotics are non-digestible nutrients metabolized by bacteria. They stimulate the growth of specific intestinal bacteria and are utilized as supplements to bolster *H. pylori* treatment [32].

S upplementation with probiotics and prebiotics in *H. pylori* therapy has demonstrated increased eradication rates and reduced side effects in patients [33, 34]. Mechanisms of probiotic action include immunological modulation, production of antimicrobial substances, inhibition of adhesion, and enhancement of mucin secretion [35, 36].

Antimicrobial peptides (AMPs), naturally produced by organisms, play a pivotal role in innate immunity. They interact with microbial cell membranes, leading to cell lysis. Synthetic AMP analogs have exhibited anti-*H. pylori* activity [37, 38]. AMPs produced by gastric epithelial cells regulate the bacterial population in the stomach, but *H. pylori* has evolved resistance mechanisms [39-41].

Present research focuses on identifying efficacious probiotic strains and evaluating their efficiency either alone or in combination with antibiotics. Discrepant results have been reported, necessitating further studies to ascertain their impact on *H. pylori* eradication rates and gut microbiota [42-47]. In summary, while alternative approaches such as probiotics, prebiotics, and antimicrobial peptides exhibit potential in *H. pylori* treatment, additional research is required to determine their effectiveness and optimal usage [37].

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are short oligopeptides possessing a positive charge, produced naturally by numerous organisms. Their role in innate immunity is essential, enabling them to defend against a variety of pathogens, including *H. pylori*. AMPs interfere with microbial cell membranes, instigating increased membrane permeability, pore formation, and leading to cell lysis. Synthetic AMP analogues, for instance, pexiganan, tilapia piscidins, and PGLa-AM1, have shown a remarkable ability to combat *H. pylori*. Bicarinalin and cathelicidins have also displayed anti-*H. pylori* activity. Despite their effectiveness, *H. pylori*

has evolved specific resistance mechanisms against host AMPs. The development of new synthetic AMP analogues and further research is actively underway [37, 38, 48-50].

Photodynamic Therapy

Photodynamic therapy (PDT) combines a photoactive molecule, termed a photosensitizer, with visible light and oxygen to generate cytotoxic reactive oxygen species (ROS). The potential of PDT as a treatment for *H. pylori* infections is currently under investigation. *H. pylori* inherently synthesizes and stores photosensitizers, making it suitable for antibacterial PDT without the requirement for external photosensitizers. In vitro research has shown significant reductions in *H. pylori* colony-forming units (CFU) following PDT using both red and blue lights. Moreover, the conjunction of PDT with antibiotics has resulted in a synergistic antibacterial effect. The use of PDT without the addition of exogenous photosensitizers has shown minimal side effects on gastric mucosa. Current research aims to refine PDT efficacy by considering tissue interactions and optical properties [51-58].

Micro- and Nanoparticles for Drug Delivery

Microparticles (MPs) and nanoparticles (NPs) have demonstrated potential in drug delivery for the treatment of microbial infections, including *H. pylori*. The small size and high surface-to-volume ratio of these particles enhance therapeutic efficacy and diminish side effects in comparison to traditional antibiotic-based treatments. Specifically, NPs can navigate physiological barriers and interact with pathogen membranes and cell walls. Drugs, such as antibiotics, can be loaded onto these particles, ensuring delivery to the infection site and protection from degradation and resistance mechanisms [57-60].

Expanding on these alternative approaches, AMPs, PDT, and micro- and nanoparticles provide potential novel treatments for *H. pylori*. Currently, research is directed towards optimizing their efficacy and suitability for clinical settings.

Microparticles and Nanoparticles for *H. pylori* Eradication

In the quest to enhance *H. pylori* eradication, microparticles and nanoparticles have come under investigation. Chitosan-based MPs and NPs have shown promise as gastric drug delivery systems, due to their biocompatibility, antimicrobial attributes, and mucoadhesiveness. Progress has been made using chitosan-based mini-tablets, nanoparticles, or hydrogels loaded with amoxicillin. Moreover, Poly (lactic-co-glycolic acid) nanoparticles possessing pH-sensitive and acid-resistant properties have been developed for targeted drug delivery to *H. pylori* infection sites. Metal nanoparticles, including gold, silver, and zinc oxide, have demonstrated good biocompatibility and anti-*H. pylori* activity. Another breakthrough was the coating of polymeric nanoparticles with *H. pylori* outer membrane proteins, which led to reduced *H. pylori* adhesion to gastric tissues. The combination of lytic bacteriophages with nanoparticles resulted in a synergistic effect, decreasing *H. pylori* colonization. Further optimization of these methods is required [61-64].

Vaccines against *H. pylori*

The development of a highly effective vaccine against *H. pylori* is perceived as a cost-effective method to prevent infection and associated diseases. Although prophylactic and therapeutic vaccines have been tested, no large-scale vaccine has been successfully produced yet. Clinical trials of different vaccine formulations have exhibited some immune responsiveness but have not consistently reduced bacterial load or stimulated protective immunity. Current research is centered on multivalent epitope-based vaccines, recombinant or fusion protein-based vaccines, and mucosal adjuvants. Oral vaccines face obstacles, but nanoparticles have shown promise in safeguarding antigens and eliciting immune responses. For instance, chitosan nanoparticles have displayed stability, enhanced immune response, and prolonged release of DNA vaccines. Immunoinformatics has also contributed to the screening of antigen targets and designing epitope-based vaccines. Vaccine development necessitates further research [65-67].

Natural Products against *H. pylori*

Natural products like plants, fruits, and spices have been explored for their anti-*H. pylori* properties. These products exhibit inhibitory effects on bacterial enzymes, possess anti-adhesive and anti-inflammatory properties, and provide bactericidal or bacteriostatic effects. Investigations have been carried out on Citrus bergamia derivatives, blueberry, grape seed extract,

mastic gum, cinnamon, ginger, curcumin, chestnut, oak honey, and propolis. However, further studies are needed to identify the specific compounds and mechanisms responsible for their activity [68-71].

Phage Therapy for *H. pylori*

The concept of phage therapy, which employs bacteriophages to target and eradicate bacterial infections, has sparked interest in treating *H. pylori*. Phages are known for their ability to selectively lyse specific bacterial strains while leaving the microbiota unharmed. Deemed safe for clinical use, phages replicate inside bacterial host cells, enabling them to target new bacterial cells. Phage therapy has proven effective in treating infections caused by pathogenic and antibiotic-resistant bacteria. Despite its potential, further research is required to translate phage therapy into a clinical application for *H. pylori* [72-76].

Interestingly, phage therapy for *H. pylori* infections has shown potential. In a study , a therapy was developed combining phage Hp ϕ with lactoferrin adsorbed on hydroxyapatite nanoparticles (NPs). This novel treatment demonstrated enhanced antimicrobial effects against *H. pylori* in human gastric cancer cells [77]. Yet, comprehensive data on phages and phage-*H. pylori* interactions in the gastric environment are lacking. The absence of sequenced phage genomes restricts our understanding of key factors like toxins, antimicrobial resistance genes, and virulence in *H. pylori* phages. Moreover, reports of endolysins present in *H. pylori* phages are nonexistent [78].

Endolysins are phage proteins responsible for breaking down bacterial cell walls and present an alternative approach in phage therapy. Endolysins show specificity to the bacterial host, and to date, bacterial resistance to endolysins hasn't been reported [79]. However, treating Gram-negative bacteria like *H. pylori* is challenging due to the presence of an outer membrane barrier. Strategies involving engineering approaches or combining lysins with weak acids have shown success in permeabilizing the outer membrane [80, 81].

CONCLUSION

The landscape for *H. pylori* eradication continues to evolve, with promising alternative approaches emerging from recent research. Antimicrobial peptides, phage therapy, nanoparticle-enhanced delivery, vaccines, and natural products represent novel strategies that are redefining the treatment modalities available for *H. pylori* infection.

Antimicrobial peptides (AMPs), both natural and synthetic, offer a new way to combat *H. pylori*. The ongoing development of synthetic AMP analogues and the further understanding of their interaction with microbial cell membranes are expected to enhance their potential as an effective therapeutic approach.

Phage therapy has also shown significant potential for *H. pylori* treatment. The ability of bacteriophages to selectively lyse specific bacterial strains could lead to more targeted therapies that do not disrupt the microbiota. The combined use of endolysins and engineered approaches presents a compelling opportunity to overcome the challenges presented by the outer membrane barrier of Gram-negative bacteria such as *H. pylori.*

Nanotechnology has emerged as a potent tool for improved drug delivery. The properties of microparticles and nanoparticles, including their small size, high surface-to-volume ratio, and ability to overcome physiological barriers, hold significant promise for enhanced therapeutic effectiveness.

Moreover, the development of a vaccine against *H. pylori* has been considered a cost-effective method to prevent infection and associated diseases. Despite various challenges, ongoing research in multivalent epitope-based vaccines and recombinant or fusion protein-based vaccines, coupled with the use of mucosal adjuvants and nanoparticles, suggests that a successful vaccine may be within reach.

Finally, natural products also offer an appealing direction for research, with their demonstrated inhibitory effects on *H. pylori* and the potential for fewer side effects compared to synthetic drugs.

However, despite these promising alternatives, further in vivo studies and well-designed clinical trials are necessary to fully understand and realize their potential. As our understanding of *H. pylori* and its resistance mechanisms expands, these targeted therapies could provide personalized treatment options that selectively deplete *H. pylori* without disrupting the normal gastric microbiome.

In this context, these alternatives represent not only a departure from the traditional antibiotic-based treatments, but also a promising pathway towards more effective and sustainable solutions for the management and eradication of *H. pylori* infections. Such advancements could significantly improve patient outcomes, reduce the societal and economic burden of these infections, and usher in a new era of personalized and effective treatments for *H. pylori*.

In summary, the research landscape for *H. pylori* eradication is expanding, with alternative approaches like phage therapy, antimicrobial peptides, nanoparticles, vaccines, and more showing great potential. However, comprehensive in vivo studies and well-structured clinical trials are crucial to fully grasp their efficacy. These targeted therapies can provide personalized treatment options that selectively deplete *H. pylori* without disrupting the normal gastric microbiome, making them exciting alternatives to broad-spectrum antibiotics and non-selective treatments for *H. pylori* infections.

Authors' Contribution

Study Conception: SÖ; Study Design: SÖ; Supervision: SÖ; Funding: N/A; Materials: N/A; Data Collection and/or Processing: SÖ; Statistical Analysis and/or Data Interpretation: SÖ; Literature Review: SÖ; Manuscript Preparation: SÖ and Critical Review: SÖ.

Conflict of interest

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