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CLINICAL MANAGEMENT, NURSING ASSESSMENT, AND EVIDENCE-BASED CARE IN THE TREATMENT OF HELICOBACTER PYLORI INFECTION-AN UPDATED REVIEW

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ABSTRACT

Background: *Helicobacter pylori* infection remains one of the most prevalent chronic bacterial infections worldwide and is a major etiological factor in chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. Increasing antimicrobial resistance has significantly reduced the effectiveness of conventional eradication regimens, necessitating the development of evidence-based treatment strategies that optimize therapeutic outcomes while minimizing treatment failure. **Aim:** This review aimed to summarize recent evidence regarding the efficacy, safety, and clinical application of current *Helicobacter pylori* eradication therapies, with particular emphasis on first-line, second-line, rescue, and adjunctive treatment approaches. **Methods:** A narrative review of contemporary clinical studies randomized controlled trials, systematic reviews, meta-analyses, and international consensus guidelines was conducted. Evidence related to triple therapy, nonbismuth and bismuth-based quadruple therapies, fluoroquinolone-containing regimens, antimicrobial resistance, acid suppression, probiotic supplementation, recurrence, and rescue treatment strategies was critically synthesized. **Results:** Conventional clarithromycin-based triple therapy demonstrated variable eradication rates ranging from 49% to 100%, whereas nonbismuth concomitant and sequential therapies generally achieved eradication rates exceeding 88%. Bismuth-containing regimens and levofloxacin-based therapies showed favorable efficacy as second-line and rescue treatments. Antimicrobial resistance, particularly to clarithromycin, metronidazole, and levofloxacin, emerged as the principal determinant of treatment failure. **Conclusion:** Contemporary management of *Helicobacter pylori* infection requires individualized, evidence-based treatment guided by regional antimicrobial resistance patterns and previous antibiotic exposure. Optimized multidrug regimens, appropriate acid suppression, and susceptibility-guided rescue therapy remain essential for maximizing eradication success and reducing disease-related complications.

KEYWORDS: *Helicobacter pylori*; eradication therapy; triple therapy; quadruple therapy; antimicrobial resistance; proton pump inhibitors; probiotics; fluoroquinolones; bismuth therapy; evidence-based care.

INTRODUCTION

Helicobacter pylori eradication continues to represent a major focus of contemporary gastroenterology research because of its substantial impact on reducing the global burden of gastrointestinal diseases and their associated complications. Over the past year, numerous high-quality studies have expanded current knowledge regarding optimal eradication strategies, treatment efficacy, antimicrobial resistance, and adjunctive therapeutic approaches. Among the most influential developments has been the publication of the updated European Consensus Guidelines on *Helicobacter pylori* management, commonly referred to as the Maastricht/Florence Consensus Report, which provides comprehensive, evidence-based recommendations for the diagnosis and treatment of *H. pylori* infection and serves as an important reference for clinical practice worldwide.[1] Recent investigations have primarily focused on evaluating the effectiveness of conventional standard triple therapy, which has historically been

considered the cornerstone of first-line treatment. However, declining eradication rates associated with increasing antimicrobial resistance have prompted extensive research into alternative therapeutic strategies. Consequently, considerable attention has been directed toward the development and assessment of optimized triple therapy regimens and non-bismuth quadruple therapies as potential first-line treatment options capable of achieving superior eradication outcomes. These therapeutic approaches have demonstrated encouraging clinical results in several patient populations and have contributed to the refinement of contemporary treatment recommendations.[1] Another significant area of advancement has involved the ongoing surveillance of antibiotic resistance patterns, which remain one of the principal determinants of treatment failure. Increasing resistance to commonly prescribed antimicrobial agents has emphasized the importance of tailoring eradication regimens according to regional susceptibility profiles and previous antibiotic exposure. In response to these challenges, investigators have explored a variety of rescue therapies for patients experiencing unsuccessful initial eradication. Particular emphasis has been placed on the evaluation of newer fluoroquinolone-based regimens, which have shown promising efficacy as salvage treatments in carefully selected patients. These developments have enhanced clinicians' ability to manage refractory *H. pylori* infections while addressing the growing challenge of antimicrobial resistance.[1]

Substantial progress has also been achieved in optimizing gastric acid suppression, a fundamental component of successful eradication therapy. Improved acid inhibition enhances antibiotic stability and activity within the gastric environment, thereby increasing bacterial eradication rates. Simultaneously, growing interest has emerged regarding adjunctive therapeutic interventions, particularly the use of probiotics. Numerous clinical investigations have examined the role of probiotic supplementation in improving treatment tolerability, reducing antibiotic-associated adverse effects, and potentially enhancing eradication success. The expanding body of evidence supporting these adjunctive therapies reflects an evolving, multifaceted approach to *H. pylori* management that extends beyond antimicrobial therapy alone.[1] Despite continuing challenges related to antimicrobial resistance and treatment optimization, there is broad consensus that successful eradication of *Helicobacter pylori* remains an essential clinical objective because of its proven role in preventing both benign and malignant gastrointestinal diseases. Effective eradication substantially reduces the incidence and recurrence of dyspepsia, peptic ulcer disease, and gastric malignancies, thereby improving long-term patient outcomes and reducing healthcare utilization. Notably, one important investigation evaluated the effect of *H. pylori* eradication on recurrent bleeding among patients with peptic ulcer disease and demonstrated an almost complete absence of ulcer rebleeding following successful eradication. These findings indicate that long-term maintenance antiulcer or antisecretory therapy is generally unnecessary once complete eradication has been achieved, highlighting the profound clinical benefits of definitive treatment and reinforcing the importance of achieving successful eradication during the initial course of therapy.[2]

Triple Therapy

Standard triple therapy consisting of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin has long been established as the conventional first-line treatment for *Helicobacter pylori* infection and remains one of the most frequently prescribed eradication regimens worldwide. The rationale for this therapeutic combination lies in the synergistic action of potent gastric acid suppression provided by the PPI, which enhances antibiotic stability and bacterial susceptibility, together with the bactericidal effects of amoxicillin and clarithromycin. For many years, this regimen achieved consistently high eradication rates and was considered the standard against which emerging therapeutic strategies were evaluated. Nevertheless, accumulating evidence has demonstrated substantial geographical variation in treatment success, largely attributable to increasing antimicrobial resistance, differences in patient adherence, genetic variations affecting drug metabolism, and regional prescribing practices. Several large-scale investigations conducted in East Asia have demonstrated that clarithromycin-based triple therapy continues to provide favorable clinical outcomes in regions where clarithromycin resistance remains relatively low. Long-term studies from Korea reported sustained eradication rates ranging between 85% and 90% over the preceding decade, supporting the continued effectiveness of this regimen in appropriately selected populations.[3,4] Comparable findings were reported in Singapore, where standard triple therapy maintained similarly high cure rates and continued to represent an effective first-line treatment option.[5] Furthermore, an investigation conducted in Thailand produced particularly encouraging results by utilizing a 14-day regimen incorporating high-dose proton pump inhibitor therapy together with long-acting clarithromycin. This optimized treatment protocol achieved a remarkable eradication rate of 100%, suggesting that extending treatment duration and optimizing acid suppression may significantly enhance therapeutic efficacy under favorable resistance conditions.[6]

In contrast, several studies conducted across Europe, Asia, and Latin America have documented considerably lower eradication rates with conventional clarithromycin-based triple therapy, raising concerns regarding its continued suitability as a universal first-line regimen. Investigations from Spain reported eradication rates that were substantially below the desired clinical threshold, reflecting the growing challenge posed by clarithromycin-resistant *H. pylori* strains.[7,8] Similar findings were observed in studies from India, México, Greece, and Japan, where treatment success ranged from

only 49% to 78%, values that fall well below the internationally accepted target eradication rate of at least 90% for first-line therapy.[9–12] These findings emphasize the importance of adapting treatment strategies according to regional antimicrobial susceptibility patterns rather than relying on a standardized therapeutic approach. The optimal duration of triple therapy has also been the subject of clinical investigation. Although extending treatment duration has frequently been associated with improved eradication rates, evidence remains inconsistent across different populations. A study conducted in Kenya compared seven-day and fourteen-day clarithromycin-based triple therapy regimens and found no statistically significant difference in eradication outcomes between the two treatment durations, suggesting that factors other than treatment length, including bacterial resistance and patient adherence, may exert a greater influence on therapeutic success in certain clinical settings.[13] These observations highlight the need for individualized treatment selection based on local epidemiological data and patient-specific considerations. Researchers have also explored pharmacological adjuncts capable of enhancing eradication success. An innovative study conducted in Israel evaluated the addition of simvastatin, a lipid-lowering medication with recognized anti-inflammatory and immunomodulatory properties, to conventional clarithromycin-based triple therapy. The findings demonstrated a significant improvement in eradication outcomes, with intention-to-treat analysis revealing successful eradication in 86% of patients receiving simvastatin compared with only 69% among those receiving placebo.[14] These results suggest that adjunctive therapies targeting host inflammatory responses may represent a promising strategy for improving treatment efficacy, although additional large-scale randomized controlled trials are required before routine clinical implementation can be recommended.

Increasing global resistance to clarithromycin has stimulated renewed interest in alternative triple therapy regimens incorporating metronidazole instead of clarithromycin. This therapeutic substitution has become particularly relevant in regions where clarithromycin resistance has compromised the effectiveness of conventional therapy. A Spanish study involving 136 patients evaluated a ten-day regimen consisting of a proton pump inhibitor, amoxicillin, and metronidazole combined with high-dose esomeprazole and reported an encouraging eradication rate of 82.4%, indicating that optimized metronidazole-based therapy may serve as an effective first-line alternative in selected populations.[15] Similar observations were reported in Japan, where investigators compared clarithromycin-based and metronidazole-based seven-day triple therapy regimens. Intention-to-treat analysis demonstrated significantly higher eradication rates with the metronidazole-containing regimen, achieving 96.4% compared with only 74.5% for clarithromycin-based therapy.[16] Furthermore, another Japanese study evaluating metronidazole-containing second-line therapy among patients previously treated with metronidazole-based triple therapy reported eradication rates exceeding 90%, reinforcing the effectiveness of carefully selected salvage treatment strategies.[17] However, the clinical success of metronidazole-based therapy is likewise influenced by regional resistance patterns. A study conducted in Tunisia failed to reproduce the favorable outcomes observed elsewhere because metronidazole resistance reached approximately 60%, substantially reducing treatment effectiveness and highlighting the critical importance of local antimicrobial surveillance when selecting eradication regimens.[18] These findings underscore that no single therapeutic protocol is universally applicable, and treatment recommendations must remain adaptable to evolving resistance profiles. Additional efforts to improve eradication success have included the evaluation of alternative antimicrobial agents. A recent Italian study investigated a ten-day regimen consisting of a proton pump inhibitor, the macrolide antibiotic miocamycin, and tinidazole. This novel combination achieved an eradication rate of 86%, representing a substantial improvement over the previously reported 57% cure rate associated with conventional triple therapy in the same clinical setting.[19] These findings illustrate the ongoing evolution of triple therapy and demonstrate that optimizing antibiotic selection according to local resistance patterns remains essential for maintaining high eradication rates and improving long-term clinical outcomes in patients with *Helicobacter pylori* infection.

Nonbismuth Quadruple Therapies

Nonbismuth quadruple therapies have emerged as highly effective alternatives to conventional triple therapy for the eradication of *Helicobacter pylori*, particularly in regions experiencing increasing resistance to clarithromycin and other commonly prescribed antibiotics. The declining effectiveness of standard triple therapy has prompted the development of multidrug treatment strategies designed to overcome antimicrobial resistance while maximizing eradication success. Among these approaches, sequential therapy, concomitant therapy, and hybrid therapy have received considerable attention because of their ability to achieve higher eradication rates across diverse patient populations. These regimens represent important advances in the management of *H. pylori* infection and have been incorporated into several contemporary international treatment guidelines. Sequential therapy has remained one of the most extensively investigated nonbismuth treatment strategies. This regimen typically consists of an initial five-day course of a proton pump inhibitor (PPI) combined with amoxicillin, followed by an additional five days of therapy consisting of a PPI together with clarithromycin and metronidazole. The theoretical advantage of this approach lies in the initial administration of amoxicillin, which weakens the bacterial cell wall and reduces bacterial load, thereby enhancing the subsequent effectiveness of the additional antibiotics. Numerous clinical studies conducted worldwide have demonstrated that sequential therapy

generally provides superior eradication rates compared with conventional triple therapy, although its efficacy varies considerably according to regional antimicrobial resistance patterns and patient characteristics. One of the most influential randomized multicenter studies evaluating sequential therapy was conducted in Taiwan, where clarithromycin resistance remains relatively low at approximately 9%. This high-quality investigation compared a 14-day sequential regimen with both a 10-day sequential regimen and a conventional 14-day clarithromycin-based triple therapy. The eradication rates achieved were 90.7%, 87.0%, and 82.3%, respectively, clearly demonstrating the superior efficacy of the extended sequential treatment protocol.[20] Similar favorable outcomes have been reported in other countries, including Italy, where eradication rates reached 92.5%, and Morocco, where sequential therapy achieved a cure rate of 84.5%, further supporting its effectiveness as a first-line therapeutic option in selected populations.[21,22]

Despite these encouraging findings, the effectiveness of sequential therapy has not been universally consistent. Several investigations conducted in Iran, India, Korea, and China have reported considerably lower eradication rates ranging from approximately 75.9% to 82.0%, indicating that the success of this regimen is highly dependent upon regional antibiotic resistance patterns, bacterial genetic variability, treatment adherence, and host-related factors.[9,23–26] These variations highlight the limitations of adopting a single treatment strategy across different geographic regions and emphasize the need for individualized therapeutic recommendations based on local epidemiological surveillance. Nevertheless, comprehensive systematic reviews evaluating sequential therapy have consistently concluded that this regimen remains significantly more effective than conventional standard triple therapy, confirming its value as an important therapeutic alternative for *H. pylori* eradication.[27,28] Concomitant therapy, also referred to as nonbismuth quadruple therapy, has subsequently gained considerable popularity because of its simplified treatment schedule and favorable clinical outcomes. Unlike sequential therapy, concomitant therapy administers all three antibiotics simultaneously in combination with a proton pump inhibitor for a treatment duration of approximately 10 to 14 days. This simplified regimen reduces the complexity associated with changing medications during treatment, thereby improving patient understanding, facilitating medication adherence, and potentially enhancing overall eradication success. Clinical investigations evaluating concomitant therapy have reported highly encouraging eradication rates across diverse populations. A study conducted in Spain demonstrated that this therapeutic approach maintained excellent effectiveness even among patients infected with clarithromycin-resistant *H. pylori* strains, achieving eradication rates approaching 90%.[29] Similarly, research performed in Thailand reported an impressive cure rate of 96% following a 10-day concomitant therapy regimen, highlighting the substantial efficacy of this multidrug approach.[30] Additional comparative studies from Greece, Korea, and Japan consistently demonstrated the superiority of concomitant therapy over standard triple therapy. Reported eradication rates reached 90.5% compared with 73.8% in Greece, 91.4% compared with 86.1% in Korea, and 94.9% compared with only 68.3% in Japan, clearly illustrating the improved therapeutic outcomes associated with concomitant treatment.[4,11,12]

Direct comparisons between sequential therapy and concomitant therapy have also provided valuable insights into their relative effectiveness. Two independent studies found that both treatment strategies achieved comparable eradication rates, although concomitant therapy demonstrated a consistent trend toward superior clinical outcomes. Reported eradication rates ranged from 80.8% versus 75.6% in one study and 88.1% versus 80.0% in another, favoring concomitant therapy in both comparisons.[31,32] Furthermore, an updated systematic review including 2,070 patients from 19 clinical studies confirmed an overall mean eradication rate of approximately 88% with concomitant therapy. This comprehensive analysis demonstrated that concomitant therapy is not only more effective than conventional triple therapy but also possesses an acceptable safety profile, reinforcing its role as a preferred first-line treatment option in many clinical settings.[33] An additional advancement in nonbismuth quadruple therapy has been the development of hybrid therapy, which combines key elements of both sequential and concomitant treatment protocols. Hybrid therapy consists of a standard 14-day sequential regimen in which amoxicillin is continued throughout the entire treatment period rather than being discontinued after the initial phase. Consequently, patients receive concomitant administration of amoxicillin together with the remaining antibiotics during the final seven days of therapy. This modification aims to maximize bacterial eradication by maintaining continuous inhibition of bacterial cell wall synthesis while simultaneously exposing the organism to multiple antimicrobial agents during the latter phase of treatment. Clinical evidence supporting hybrid therapy has been encouraging. A study conducted in Iran demonstrated significantly higher eradication rates with hybrid therapy compared with conventional sequential therapy, achieving success rates of 89.5% and 76.7%, respectively, thereby indicating that prolonged amoxicillin administration may contribute to improved therapeutic efficacy.[23] Further innovation has also been demonstrated through the development of novel concomitant regimens. Investigators from Australia evaluated a unique combination consisting of a proton pump inhibitor, amoxicillin, rifabutin, and ciprofloxacin, achieving an impressive eradication rate of 95.2%. Among patients with penicillin allergy, amoxicillin was successfully replaced with bismuth without significantly compromising treatment efficacy, resulting in an eradication rate of 94.2%.[34] These findings illustrate the

continuing evolution of nonbismuth quadruple therapies and emphasize the importance of developing flexible, evidence-based treatment strategies capable of addressing the growing global challenge of antibiotic-resistant *Helicobacter pylori* infection.

Bismuth-Based Therapy

Bismuth-based therapy remains an important component of *Helicobacter pylori* eradication strategies, particularly in regions where resistance to clarithromycin and metronidazole has significantly reduced the effectiveness of conventional treatment regimens. The unique antimicrobial activity of bismuth compounds, combined with their protective effects on the gastric mucosa, has contributed to their continued clinical value in both first-line and rescue treatment protocols. Bismuth-containing regimens are especially recommended for patients with previous treatment failure, those living in areas with high antibiotic resistance, or individuals who cannot receive clarithromycin-based therapy. Recent clinical investigations have continued to evaluate the efficacy of various bismuth-containing regimens, treatment durations, and alternative therapeutic combinations in an effort to optimize eradication outcomes. Among first-line treatment approaches, a pilot study conducted among Hispanic patients in the United States demonstrated exceptionally favorable outcomes with a classical 14-day bismuth-based quadruple therapy. Per-protocol analysis revealed an eradication rate of 97.1%, highlighting the remarkable effectiveness of prolonged bismuth-containing treatment in this patient population.[35] However, the study also demonstrated that shortening the duration of therapy to ten days or less resulted in a significant decline in eradication success, emphasizing the critical importance of adequate treatment duration for achieving optimal clinical outcomes. These findings support current recommendations favoring extended treatment courses to maximize bacterial eradication and reduce the likelihood of therapeutic failure. Alternative bismuth-containing treatment strategies have also shown encouraging results. A study conducted in Turkey evaluated a modified 14-day bismuth-based sequential therapy and reported an eradication rate of 81% according to intention-to-treat analysis.[36] Although this success rate was lower than that observed in the American pilot study, it nevertheless demonstrated that modified sequential regimens incorporating bismuth remain effective therapeutic options, particularly in populations affected by increasing antimicrobial resistance. Such findings further reinforce the versatility of bismuth-containing therapies and their adaptability to different clinical settings.

Researchers have also explored alternative gastroprotective agents capable of replacing bismuth in eradication protocols. Ecabet sodium, an antiulcer medication with mucosal protective properties, has been investigated as a potential substitute in regions where bismuth availability may be limited. A study conducted in an area of China characterized by high levels of antibiotic resistance compared ecabet sodium-based therapy with conventional bismuth-containing treatment. The results demonstrated nearly identical eradication rates, with intention-to-treat analyses showing cure rates of 68.4% for ecabet sodium and 68.0% for bismuth-based therapy.[37] Although these eradication rates were relatively modest, the findings suggest that ecabet sodium may represent a potential alternative in selected circumstances, although further research is needed to establish its role within standard treatment recommendations. Bismuth-containing regimens have also demonstrated considerable value as second-line or rescue therapies following unsuccessful initial eradication. A Korean study evaluating different treatment durations found eradication rates of 83.5% for a one-week course and 87.7% for a two-week course of bismuth-based therapy, indicating that prolonged treatment may provide modest improvements in eradication success among patients requiring salvage therapy.[38] Similarly, a study from Taiwan assessed bismuth-containing regimens incorporating either levofloxacin or metronidazole and reported comparable eradication rates of 78.9% and 79.7%, respectively, suggesting that both antibiotics may be effectively combined with bismuth in rescue treatment protocols.[39] Additionally, investigators in Iran evaluated a second-line bismuth-containing regimen combined with furazolidone and achieved an eradication rate of 80.6%, further expanding the range of potential therapeutic options available for managing treatment-resistant *H. pylori* infection.[40]

Studies Including Fluoroquinolones

Fluoroquinolone-based therapies have emerged as important alternatives in the treatment of *Helicobacter pylori* infection, particularly in response to the growing prevalence of resistance to clarithromycin and metronidazole. Among the fluoroquinolones, levofloxacin has received the greatest attention because of its broad-spectrum antimicrobial activity and its versatility in various eradication regimens. It has been investigated extensively as a component of first-line and second-line therapies and has been incorporated into triple, sequential, and concomitant treatment protocols. Although its overall effectiveness has been encouraging, treatment success remains highly dependent on local antimicrobial resistance patterns, treatment duration, and the susceptibility of *H. pylori* strains to fluoroquinolone antibiotics. Several clinical studies have evaluated levofloxacin-containing triple therapy as a first-line treatment option. Investigations conducted in China and India demonstrated eradication rates of 85.5% and 78.1%, respectively, using seven-day treatment regimens, indicating that short-course levofloxacin-based therapy can provide satisfactory clinical outcomes in selected populations.[26,41] Likewise, a study from Spain reported an eradication rate of 82.8% following a ten-day levofloxacin-containing triple regimen.[42] Despite these favorable results, both the Chinese and Spanish studies found no statistically significant differences between

conventional clarithromycin-based triple therapy and levofloxacin-based triple therapy, suggesting that the latter may serve as an effective alternative rather than a clearly superior first-line option.[26,42] These findings indicate that treatment selection should be guided primarily by regional resistance profiles and individual patient characteristics rather than by expectations of universally improved efficacy.

Levofloxacin has also been evaluated as a component of sequential and concomitant treatment strategies. A ten-day sequential regimen incorporating levofloxacin achieved an eradication rate of 82.8%, demonstrating its potential as an alternative multidrug approach for *H. pylori* management.[26] Furthermore, an Italian study compared a five-day concomitant regimen with a ten-day sequential regimen and found nearly identical eradication rates of 92.2% and 93.3%, respectively.[43] Importantly, the shorter concomitant regimen was associated with substantially lower treatment costs while maintaining equivalent clinical efficacy. These findings suggest that carefully designed fluoroquinolone-containing multidrug regimens may improve treatment efficiency, enhance patient adherence through shorter therapy duration, and reduce healthcare expenditures without compromising eradication success. The role of levofloxacin has been particularly well established in second-line or rescue therapy following failure of initial eradication treatment. A long-term study from Spain demonstrated stable eradication rates of 73.8% with levofloxacin-based triple therapy over a five-year period, indicating sustained effectiveness despite evolving treatment practices.[44] Similar results were observed in Taiwan, where a one-week levofloxacin-containing triple regimen achieved an eradication rate of 78.1%, compared with 75.0% for a tetracycline-based regimen, suggesting comparable efficacy between these alternative rescue strategies.[45] These findings support the continued use of levofloxacin-containing therapy as an important option for patients who fail conventional first-line treatment. Treatment duration has also been shown to influence the effectiveness of levofloxacin-based regimens. A Chinese investigation reported that extending triple therapy to fourteen days increased eradication rates to 86.3%, demonstrating the potential benefit of prolonged antibiotic exposure.[46] However, the same study identified a high prevalence of levofloxacin resistance, affecting approximately 32% of patients. This resistance had a profound impact on treatment success, with eradication rates reaching 92% among patients harboring levofloxacin-susceptible strains but declining dramatically to only 33% in those infected with resistant organisms.[46] These findings emphasize that antimicrobial susceptibility remains one of the strongest determinants of therapeutic success and highlight the importance of susceptibility-guided treatment whenever feasible.

Evidence from systematic reviews has further supported the role of levofloxacin in rescue therapy. A meta-analysis comparing levofloxacin-based triple therapy with conventional quadruple therapy for second-line eradication demonstrated superior outcomes with the levofloxacin-containing regimen, reporting eradication rates of 76.5% compared with 67.4% for quadruple therapy[47] These results reinforce the value of levofloxacin as an effective salvage treatment and support its inclusion in evidence-based clinical guidelines for patients with persistent *H. pylori* infection. Beyond levofloxacin, other fluoroquinolone antibiotics have also been investigated as components of eradication therapy. An Italian study demonstrated that adding bismuth to a ten-day moxifloxacin-based triple regimen significantly improved eradication rates from 77% to 92%, illustrating the beneficial synergistic effect of combining bismuth with fluoroquinolone-containing therapy.[48] Similarly, investigators in China reported that incorporating furazolidone into a levofloxacin-based triple regimen increased eradication success from 67% to 86%, suggesting that carefully selected combination therapies may enhance bacterial eradication in areas with challenging resistance profiles.[49] Additionally, laboratory investigations conducted in Taiwan evaluated the antimicrobial activity of gemifloxacin, a newer fluoroquinolone, and found that it demonstrated greater in vitro activity against *H. pylori* than levofloxacin, with the potential to overcome certain forms of quinolone resistance.[50] Although these findings remain preliminary, they suggest that newer fluoroquinolones may provide promising therapeutic alternatives as antimicrobial resistance continues to evolve.

Second-Line Therapy and Rescue Therapy

The management of persistent *Helicobacter pylori* infection following unsuccessful initial treatment remains a significant clinical challenge because repeated treatment failure increases the risk of chronic gastritis, peptic ulcer disease, gastric mucosal atrophy, and gastric malignancy. Consequently, evidence-based selection of second-line and rescue therapies has become an essential component of modern *H. pylori* management. The primary objective of second-line treatment is to achieve successful bacterial eradication while minimizing the likelihood of further antimicrobial resistance. This goal requires careful consideration of the antibiotics previously administered, regional resistance patterns, patient adherence, and individual clinical characteristics. Current treatment recommendations emphasize that repeating the same first-line regimen should generally be avoided because previously exposed bacteria are more likely to have developed resistance to one or more antimicrobial agents. Instead, second-line therapy should include at least one antibiotic that has not been used during the initial treatment course. This strategy reduces the probability of persistent resistance and improves the likelihood of successful eradication. Several therapeutic approaches have demonstrated acceptable efficacy as second-line treatment options, including quinolone-based regimens, bismuth-containing quadruple therapies, and other multidrug combinations. The choice among these

regimens largely depends on the composition of the initial treatment and the anticipated resistance profile of the infecting *H. pylori* strain. The updated Maastricht IV Consensus Guidelines recommend that patients whose initial treatment consisted of a proton pump inhibitor (PPI) combined with clarithromycin should receive either a bismuth-containing quadruple regimen or a levofloxacin-containing triple therapy as second-line treatment.[1] These recommendations are supported by extensive clinical evidence demonstrating that both therapeutic strategies achieve satisfactory eradication rates while avoiding repeated exposure to clarithromycin. By introducing antibiotics with different mechanisms of action, these regimens improve bacterial susceptibility and reduce the likelihood of persistent infection. The individualized selection of second-line therapy therefore represents an important principle in contemporary evidence-based management of *H. pylori* infection.

When both first-line and second-line treatments fail, patients require rescue therapy, often referred to as third-line treatment. Rescue therapy is particularly challenging because repeated exposure to antibiotics substantially increases the probability of multidrug-resistant *H. pylori* strains. Current European guidelines recommend that third-line treatment should ideally be guided by antimicrobial susceptibility testing performed on gastric biopsy specimens obtained during upper gastrointestinal endoscopy.[1] Culture-based susceptibility testing enables clinicians to identify the most effective antimicrobial agents for each individual patient and avoids the unnecessary use of ineffective antibiotics. This personalized approach has gained increasing recognition as an important strategy for maximizing eradication success while promoting responsible antimicrobial stewardship. Several recent investigations have demonstrated the clinical value of susceptibility-guided rescue therapy. A study conducted in China evaluated four different bismuth-based quadruple regimens containing various combinations of amoxicillin, tetracycline, furazolidone, and metronidazole. Despite previous treatment failures and the presence of metronidazole resistance, all four regimens achieved eradication rates exceeding 90%, highlighting the effectiveness of carefully selected multidrug combinations in difficult-to-treat patients.[51] Similar success was reported in Taiwan, where individualized treatment regimens were selected according to antimicrobial resistance profiles determined by polymerase chain reaction (PCR) genotyping. Eradication rates reached 78.9% among patients receiving clarithromycin-based sequential therapy, 92.2% for those treated with levofloxacin-based sequential therapy, and 71.4% for patients receiving tetracycline-containing regimens.[52] These findings demonstrate that molecular diagnostic techniques can facilitate personalized treatment selection and substantially improve clinical outcomes.

Further evidence supporting culture-guided therapy has been provided by investigators in Italy. Using culture-based antimicrobial susceptibility testing to guide rescue treatment, eradication rates reached 90% with levofloxacin-containing triple therapy and 88.6% with rifabutin-based triple therapy, confirming the effectiveness of individualized therapeutic strategies for patients with refractory *H. pylori* infection.[53] Interestingly, another investigation suggested that an empirically selected third-line regimen achieved an exceptionally high eradication rate of 99.5%, indicating that carefully designed empirical treatment protocols may also produce excellent clinical outcomes in selected settings where susceptibility testing is unavailable.[54] Nevertheless, susceptibility-guided therapy remains the preferred approach whenever feasible because it minimizes unnecessary antibiotic exposure and supports antimicrobial stewardship. A variety of additional rescue regimens have also been investigated for patients with repeated eradication failure. In China, a third-line combination of levofloxacin and rifaximin achieved successful eradication in approximately 65% of patients who had previously failed both standard triple therapy and bismuth-containing quadruple therapy.[55] Korean investigators compared rifabutin-based triple therapy with levofloxacin-containing treatment and found superior eradication rates with the rifabutin regimen, achieving 71.4% compared with 57.1%, respectively[56] Similar outcomes were observed in Italy, where third-line levofloxacin-based therapy achieved eradication in 67.2% of patients, while a ciprofloxacin-containing triple regimen combined with a proton pump inhibitor and metronidazole resulted in a 65% cure rate.[57,58] These studies demonstrate that multiple antimicrobial combinations remain available for patients requiring advanced rescue therapy, although treatment success generally declines following repeated eradication failures. The development of newer fluoroquinolones has also expanded the therapeutic options available for refractory infection. Two studies conducted in Japan evaluated sitafloxacin, a next-generation fluoroquinolone with enhanced antimicrobial activity against resistant *H. pylori* strains. A pilot investigation demonstrated an eradication rate of 75% with sitafloxacin-based triple therapy.[59] Subsequently, a multicenter clinical trial reported that sitafloxacin-containing treatment significantly outperformed levofloxacin-based therapy, achieving eradication rates of 70% compared with only 43.1%, respectively.[60] These findings suggest that newer antimicrobial agents may offer improved effectiveness against resistant organisms and represent promising alternatives for difficult-to-treat infections.

Alternative treatment strategies have also been explored for selected patient populations. A Japanese study demonstrated that high-dose dual therapy consisting of a proton pump inhibitor and amoxicillin administered for fourteen days achieved an eradication rate of 63%, with particularly favorable outcomes observed among patients with lower pretreatment urea breath test values,

suggesting a smaller bacterial burden.[61] Although the overall success rate was lower than that reported for multidrug rescue regimens, this simplified approach may be suitable for carefully selected patients in whom minimizing antibiotic exposure is desirable. For patients experiencing multiple treatment failures, fourth-line therapy may become necessary. Rifabutin has been investigated as a fourth-line therapeutic agent in several European studies. Investigations conducted in Italy and Spain, including the largest reported series involving 100 patients, demonstrated eradication rates of approximately 50% with rifabutin-containing regimens.[62,63] Although these success rates are lower than those achieved with earlier treatment lines, rifabutin remains an important option for highly refractory *Helicobacter pylori* infection when alternative therapies have been exhausted. Overall, current evidence supports an individualized, susceptibility-guided approach to second-line and rescue therapy, emphasizing the importance of antibiotic stewardship, regional resistance surveillance, and personalized treatment selection to maximize eradication success and improve long-term clinical outcomes.

Antimicrobial Resistance, Acid Inhibition, Probiotics, and Recurrence

Antimicrobial resistance remains one of the greatest challenges to the successful eradication of *Helicobacter pylori*. A large multicenter European study reported resistance rates of 17.5% for clarithromycin, 14.1% for levofloxacin, and 34.9% for metronidazole, while resistance to amoxicillin, tetracycline, and rifabutin remained extremely low. The study also demonstrated a significant association between outpatient antibiotic consumption and the development of bacterial resistance, emphasizing the importance of antimicrobial stewardship.[64] Resistance rates were even higher in Asia. In China, resistance reached 21.5% for clarithromycin, 95.4% for metronidazole, and 20.6% for levofloxacin, with more than one-quarter of patients exhibiting multidrug resistance.[65] Similarly, Korea reported increasing resistance to amoxicillin (14.9%), clarithromycin (23.7%), and levofloxacin (28.1%) compared with previous years.[66] In contrast, a study from Senegal found no resistance to amoxicillin or tetracycline and only 1% resistance to clarithromycin, although metronidazole resistance remained very high at 85%.[67] Advances in acid suppression have also contributed to improved eradication strategies. A pilot study demonstrated that the histamine H_2-receptor antagonist latifudine achieved eradication rates comparable to proton pump inhibitor (PPI)-based therapy while reducing treatment costs.[68] Although twice-daily PPI administration remains the standard approach, esomeprazole administered once daily demonstrated superior efficacy compared with pantoprazole in a Taiwanese study.[69] Furthermore, a meta-analysis confirmed that second-generation PPIs, particularly esomeprazole and rabeprazole, achieved higher eradication rates than first-generation PPIs, supporting their preferential use in eradication regimens.[70]

The use of probiotics as adjunctive therapy has attracted considerable attention because of their potential to enhance eradication success and reduce treatment-related adverse effects. Several studies demonstrated significant improvements in eradication rates when probiotics, particularly *Lactobacillus* species, were combined with standard antibiotic therapy. Chinese investigators reported that supplementation with *Lactobacillus acidophilus* increased eradication rates from 61.5% to 81.6%[71], while a randomized trial in Iranian children found that probiotic supplementation improved eradication from 69% to 90%.[72] Likewise, supplementation with *Lactobacillus reuteri* improved both treatment efficacy and tolerability during second-line levofloxacin-based therapy.[73] However, other studies from Iran, Italy, and Brazil failed to demonstrate significant improvements in eradication rates despite consistently reporting reductions in antibiotic-associated adverse events such as diarrhea and nausea, which contributed to better treatment adherence.[74–79] Experimental evidence also suggested that certain probiotic strains may directly suppress *H. pylori* growth and reduce gastric inflammation even without concurrent antibiotic therapy.[80] Overall, a meta-analysis of ten clinical trials demonstrated that probiotic supplementation significantly increased eradication success while substantially reducing treatment-related side effects, supporting its role as a valuable adjunct to standard therapy.[81] Recurrence of *H. pylori* infection remains an important concern following successful eradication. A multicenter study conducted in Latin America reported a recurrence rate of 11.5%, which was higher than previously documented. Recurrence was significantly associated with geographic location, poor adherence to the initial treatment regimen, and the presence of children within the household, suggesting that both behavioral and environmental factors contribute to reinfection and highlighting the importance of patient education and adherence to prescribed therapy.[82]

CONCLUSION

Successful eradication of *Helicobacter pylori* remains a fundamental objective in preventing peptic ulcer disease, gastric malignancy, and other infection-related complications. Current evidence demonstrates that the effectiveness of eradication therapy depends largely on regional antimicrobial resistance patterns, appropriate antibiotic selection, adequate acid suppression, and patient adherence. Conventional triple therapy is no longer universally reliable, whereas nonbismuth and bismuth-containing quadruple regimens provide superior outcomes in many settings. Fluoroquinolone-based and susceptibility-guided rescue therapies offer valuable options following treatment failure. Adjunctive probiotic supplementation may improve treatment tolerance and, in selected patients, enhance eradication success. Future management should emphasize personalized, evidence-based therapeutic strategies supported by continuous

surveillance of antimicrobial resistance to optimize long-term clinical outcomes.

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