

# *Helicobacter pylori* Eradication: Sequential and Traditional Therapy

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**Abstract:** Treatment of *Helicobacter pylori* infection is indicated in a number of medical conditions, including peptic ulcer disease and localized gastric lymphoma. Antimicrobial-based triple therapy is the standard treatment used in most countries throughout the world, but its success rate has declined in many countries to the point where alternative and salvage therapies such as levofloxacin and rifabutin have gained importance in clinical practice. Sequential therapy is a newly described regimen that has been shown to be superior to triple therapy in some studies. In this article, we discuss current treatment strategies for *H. pylori* infection.

**A**lthough the prevalence of *Helicobacter pylori* infection has been falling in developed countries, challenges with eradication have increased as the prevalence of resistant strains of *H. pylori* has risen. The prevalence of resistant strains of *H. pylori* in different regions of the world has recently been summarized by Vakil and Megraud.<sup>1</sup> Clarithromycin resistance is common in North America and Southern Europe (found in 13% of patients in the United States<sup>2</sup>), whereas metronidazole resistance is common in Asia. The *Helicobacter pylori* Antimicrobial Resistance Monitoring Program is a prospective, multicenter US network that tracked US rates of *H. pylori* antimicrobial resistance. Of the 347 clinical *H. pylori* isolates collected between 1998 and 2002, 101 isolates (29.1%) were resistant to 1 antimicrobial agent and 17 (5%) were resistant to 2 or more antimicrobial agents. Eighty-seven isolates (25.1%) were resistant to metronidazole, 45 (12.9%) to clarithromycin, 3 (0.9%) to amoxicillin, and none to tetracycline.<sup>2</sup> Clarithromycin resistance is encountered infrequently in Scandinavia (1–3%).<sup>3–5</sup> In Iran, the prevalence of clarithromycin resistance is 16.7% and the prevalence of metronidazole resistance is 57.5%.<sup>6</sup> A study from Kuwait reported the same high rate of metronidazole resistance, but no clarithromycin resistance was detected.<sup>7</sup> Little information is available regarding Africa, where one study reported that the prevalence of clarithromycin resistance was 6.4% and all strains were resistant to metronidazole.<sup>8</sup> Antimicrobial resistance is, therefore, a global

## Keywords

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problem, but the drug or drugs to which *H. pylori* has become resistant vary in different regions of the world.

### Delivery of Antibiotics to *H. pylori*

Antimicrobials used for *H. pylori* treatment were originally developed for the treatment of other infections and are not specifically designed to achieve high concentrations in gastric mucus where *H. pylori* lives. Therefore, a variety of methods must be used to achieve high drug concentrations in *H. pylori*'s environment. These methods include combining antimicrobial treatment with proton pump inhibitors to improve drug concentrations in gastric juice and using combinations of antimicrobial drugs to increase the likelihood of success.

#### *Maintaining Sufficient Concentrations of Antimicrobials in the Gastric Mucus*

A major clinical problem with antimicrobial treatment regimens for *H. pylori* infection is adherence to the treatment regimen. Intolerable side effects associated with prolonged courses of treatment can lead to premature discontinuation of therapy and the development of resistant strains of *H. pylori*. Quadruple therapies, which require ingestion of medications four times daily, can cause problems with adherence because of their combination with proton pump inhibitors, which must be taken only twice daily.<sup>9</sup> Adherence to sequential therapy (to be discussed later) may also be a problem in routine practice. Compliance packs can help with adherence and require further consideration with sequential therapy.

There have been no new developments in drug delivery for *H. pylori* in recent years. Ranitidine bismuth citrate, a drug that is no longer available in the United States, was developed specifically for treatment of *H. pylori*. It disintegrated rapidly in the stomach, allowing bismuth to be delivered to the *H. pylori*.<sup>10</sup>

#### *Gastric pH, Emptying, and Other Physiologic Variables*

The gastric mucus layer is a mechanical barrier that limits the penetration of antimicrobials and, therefore, their effect on *H. pylori*. Strategies to decrease the thickness and the viscosity of the mucus layer have been evaluated in experimental studies. In animals, the use of agents such as Pronase that decrease the thickness of the mucus layer have been shown to improve delivery of antimicrobials, but there are no clinical studies of their use at this time.<sup>11</sup> Proton pump inhibitors play an important role in treatment regimens for *H. pylori* infection. By decreasing the volume of gastric juice, they raise antimicrobial concentrations in the gastric juice. Proton pump inhibitors may also decrease the viscosity of the gastric mucus

layer, thereby increasing its permeability. Inhibition of acid secretion may also contribute to improved stability of antimicrobials in the stomach. Clarithromycin is very sensitive to degradation by gastric acid and has a half-life of less than 1 hour at a pH of 2.<sup>12,13</sup> Metronidazole is very stable in gastric juice, regardless of pH, with a half-life of over 800 hours. Amoxicillin is less stable at low pH, but its half-life is still 15 hours at a pH of 2.

### Key Agents in Antimicrobial Regimens for *H. pylori*

Key agents are drugs that form the cornerstone of a treatment regimen. Key agents in eradication regimens for *H. pylori* are amoxicillin, clarithromycin, and metronidazole or tinidazole. All successful treatment regimens for *H. pylori* contain one or more of these agents. Combinations of drugs that contain none of these agents have poor efficacy. Of the 3 key drugs, amoxicillin is the most important agent and is the most widely used in different combinations because resistance to this agent develops very rarely in clinical practice. Resistance to metronidazole and clarithromycin is much more important clinically, and resistance to one of these agents is often the cause of failed therapy. Clarithromycin resistance is generally caused by a mutation in the organism that prevents binding of the antibiotic to the ribosome of *H. pylori*, thereby preventing interruption of bacterial protein synthesis, which is the primary mechanism of action of clarithromycin.<sup>1</sup> There is cross-reactivity among different macrolides, and clarithromycin resistance may develop with exposure to any macrolide.

Metronidazole is a prodrug that must be reduced in the cell to have an adverse effect on bacterial DNA. Frameshift mutations in a gene called *rdxA* have been associated with metronidazole resistance, but mutations in other genes may also be responsible.<sup>14</sup> A recent analysis of published studies found a 70% decline in eradication rates if clarithromycin resistance was present and a clarithromycin-containing regimen was used.<sup>15</sup> Nitroimidazole resistance causes an efficacy reduction of 50% with triple and quadruple therapies.<sup>15</sup>

### Sequential Therapy and Resistance

The sequential treatment regimen that is described in more detail below contains all three of the key antimicrobial agents that are currently available. This regimen, therefore, has the potential to demonstrate efficacy in the setting of antimicrobial resistance. Only limited data are available at this point, but they suggest that this treatment may be effective in patients with clarithromycin-resistant strains of *H. pylori*.<sup>16</sup>

## Current Recommendations for Treatment of *H. pylori*

Recent recommendations of the European *H. pylori* study group and the American College of Gastroenterology recommend triple therapy (proton pump inhibitor + amoxicillin + clarithromycin) as the initial treatment for *H. pylori* infection.<sup>17,18</sup> Quadruple therapy (proton pump inhibitor + bismuth + metronidazole + tetracycline) is an alternate initial strategy. These treatment regimens have limitations that are discussed in more detail below, and it is possible that sequential therapy may replace these treatments as a first-line therapy.<sup>19</sup>

### Initial Treatment Regimens

#### *Proton Pump Inhibitor Triple Therapy*

The most recent studies with proton pump inhibitor triple therapy performed in the United States are now several years old and demonstrated very low eradication rates.<sup>20-25</sup> It is likely that eradication rates have declined further since then. In one study, the intent-to-treat eradication rate was 65%, with confidence intervals (CIs) ranging from 57–73%.<sup>24</sup> In another study, the intent-to-treat eradication rate was 78%, with CIs ranging from 72–84%.<sup>25</sup>

#### *Proton Pump Inhibitor Therapy in Clinical Practice*

The continued use of proton pump inhibitor triple therapy has been questioned by some, and an extreme view is that this treatment is “unethical” due to its low efficacy.<sup>26</sup> Current guidelines continue to recommend triple therapy, which is the most widely used treatment in much of the western world,<sup>27,28</sup> as the preferred initial therapy. Three studies provide evidence that triple therapy can still be an effective regimen as a component of a coordinated treatment strategy for *H. pylori*. In an Irish study, 3,280 patients received proton pump inhibitor triple therapy, which was effective in 2,530 patients (77%). Bismuth-based quadruple therapy or an alternative triple therapy was successful in 56% of 270 patients who were treatment failures with the initial therapy. Subsequent eradication attempts using rifabutin-based regimens (n=34) and furazolidone-based regimens (n=10) were successful in 38% and 60% of patients, respectively. This trial suggested that it is possible to achieve successful eradication in the majority of patients using traditional treatments. In another pragmatic trial performed in Greece, patients were initially treated with proton pump inhibitor triple therapy, failures were given quadruple therapy, and patients failing both treatments were given levofloxacin triple therapy.<sup>29</sup> Using this strategy, among the 540 patients receiving treatment, 484 had successful eradication, 47 were withdrawn from

the study or lost to follow-up, and 9 remained infected (intent-to-treat eradication rate: 89.6%). A study from Spain with a population of 500 patients reported a high success rate of 99.5% when traditional triple therapy was used and salvage therapies were administered to those who failed triple therapy.<sup>30</sup>

The major points to be taken away from recent data on triple therapy are: initial treatment may fail in as many as 25–30% of patients; all patients should be tested after treatment to confirm eradication; and a salvage plan should be established for treatment failures. Furazolidone is a carcinogen and mutagen and has been withdrawn in Europe and the United States. Its use is no longer recommended.

### Quadruple Therapy

Quadruple therapy (bismuth + metronidazole + tetracycline + proton pump inhibitor, administered for 7–10 days) is a particularly useful treatment in areas where metronidazole resistance is low and clarithromycin resistance is high. As this therapy is an inexpensive regimen, it is often preferred in situations where the cost of therapy is the main concern. A large randomized controlled trial compared 7-day quadruple therapy (bismuth + metronidazole + tetracycline + proton pump inhibitor) with 7-day triple therapy. Eradication rates were similar in proton pump inhibitor triple therapy (78%) and quadruple therapy (82%).<sup>31</sup> In another randomized controlled trial in Spain, 7-day proton pump inhibitor triple therapy was similar to quadruple therapy in the eradication of *H. pylori*.<sup>32</sup>

A single capsule preparation of bismuth biscalcitate with metronidazole and tetracycline has made quadruple therapy easier for patients<sup>21</sup> by reducing the total number of pills that patients must take and, therefore, simplifying the regimen considerably. Results have been promising, with an eradication rate of 93% by intent-to-treat analysis in Europe and 87.7% in the United States for 10-day therapy.<sup>21,33</sup> In the US trial, the results were comparable to those with a 10-day proton pump inhibitor triple therapy, though the trial was performed in 1998.<sup>21</sup> A major disadvantage is that 3 tablets are still needed to be taken 4 times daily. In addition, a proton pump inhibitor must be taken twice daily. Regimens requiring such frequent administration of medication are associated with poor adherence.

Despite the promotion of quadruple therapy as an alternative to triple therapy, the evidence to support this strategy is limited. A recent meta-analysis found only 4 studies of sufficient quality to allow comparisons between quadruple therapy and triple therapy and concluded that there was no statistically significant difference between proton pump inhibitor triple therapy and quadruple therapy.<sup>34</sup> At the last Maastricht international consensus

conference of experts on *H. pylori*, a proposal was made that proton pump inhibitor triple therapy be replaced with quadruple therapy, but it failed to generate any meaningful support, suggesting that experts continue to have reservations regarding this form of therapy.<sup>17</sup> This therapy needs consideration in regions where clarithromycin resistance rates are high and metronidazole resistance rates are low.

### Nonbismuth Quadruple Therapies

Studies performed in the late 1990s in Europe and Japan suggested that a short course of therapy lasting 3–5 days in duration may be effective with quadruple treatment regimens that did not contain bismuth. In one such study, performed between 1997 and 1999, patients received a 5-day treatment with 3 antibiotics: amoxicillin 1 g twice daily, clarithromycin 250 mg twice daily, and metronidazole 400 mg twice daily, along with a proton pump inhibitor administered twice daily.<sup>35</sup> Recommendations for this form of therapy have resurfaced recently with a new name: concurrent or concomitant therapy. However, the available data are more than one decade old and resistance patterns have changed considerably in the interval. Furthermore, there are no double-blind, randomized controlled trials with this regimen, limiting the quality of the available evidence.

### Sequential Therapy

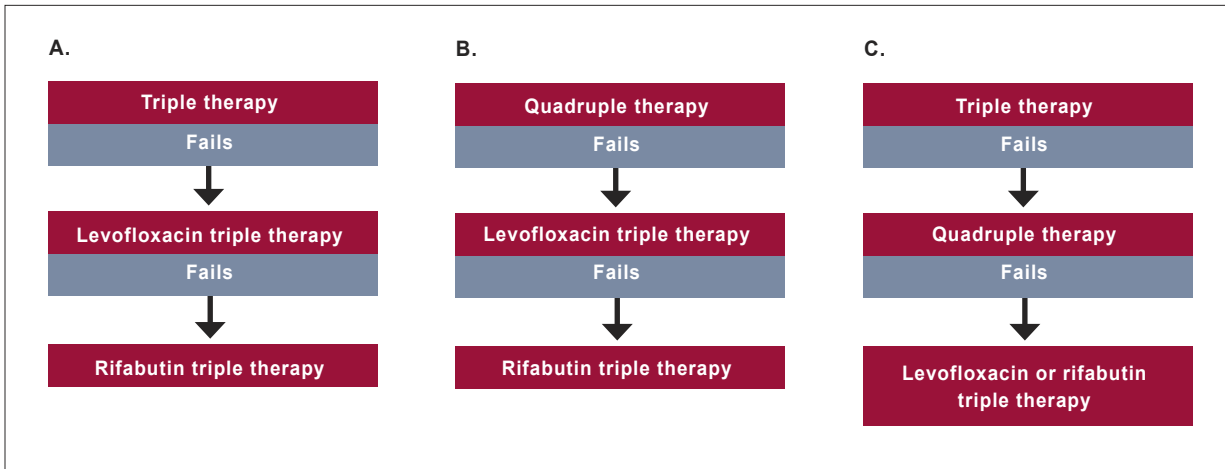
Sequential therapy is a novel treatment method. Instead of administering the antimicrobials all at once, they are administered in sequence. This can reduce side effects by limiting patient exposure to individual antibiotics. This treatment strategy was developed based upon observations made when dual drug therapies (proton pump inhibitor + amoxicillin) were still in use. Studies conducted during that period demonstrated that the eradication rate achieved with a therapeutic strategy of initially administering 14-day dual therapy (proton pump inhibitor + amoxicillin) followed by 7-day triple therapy in individuals who failed the original therapy was significantly better than the reverse sequence (7-day triple therapy as an initial strategy with 14-day dual therapy for failures).<sup>36</sup> The sequential regimen that has been best described is a 10-day treatment consisting of a proton pump inhibitor and amoxicillin 1 g (both twice daily) administered for the first 5 days followed by triple therapy consisting of a proton pump inhibitor, clarithromycin 500 mg, and tinidazole 500 mg (all twice daily) for the remaining 5 days. A recent randomized controlled trial compared sequential therapy and standard triple therapy<sup>16</sup> in 300 patients with *H. pylori* infection, who were randomized to sequential or triple therapy. Sequential therapy was

more effective in patients with clarithromycin-resistant strains, a difference that was statistically significant (89% vs 29%;  $P=.0034$ ). A recent meta-analysis of 10 trials found an eradication rate of 93.4% (95% CI, 91.3–95.5) with sequential therapy compared to an eradication rate of 76.9 (95% CI, 71–82.8) with proton pump inhibitor triple therapy. However, several errors were identified in the meta-analysis in subsequent correspondence.<sup>37,38</sup> Much of the data from randomized controlled trials come from Italy, but data from an open-label study in Spain also suggest that the eradication rate in routine clinical practice may be comparable to the Italian data (n=139; eradication rate, 84.2%, 95% CI, 77–90%).<sup>39</sup> In another recent study from Taiwan, still in preliminary form, the eradication rate in 129 patients was 89%.<sup>40</sup> The limited data available suggest that sequential treatment appears to maintain a high level of efficacy in patients with clarithromycin resistance. In a large randomized trial, the eradication rate was 89% in patients with *H. pylori* infection that was resistant to clarithromycin who were treated with sequential therapy compared to 29% in those treated with triple therapy. However, the number of patients with resistance was small.<sup>16</sup>

### Salvage Therapies

Levofloxacin and rifabutin are treatments for patients in whom standard treatments fail. A recent meta-analysis compared bismuth quadruple therapy (bismuth + tetracycline + metronidazole + proton pump inhibitor) with triple therapy using levofloxacin (levofloxacin 500 mg daily + amoxicillin 1 g twice daily + proton pump inhibitor twice daily) in patients who failed eradication with standard triple therapy.<sup>41</sup> Levofloxacin triple therapy was better tolerated than quadruple therapy and had better eradication rates (81% vs 70%; odds ratio, 1.80; 95% CI, 0.94–3.46). Ten-day levofloxacin triple therapy was superior to 7-day therapy, and the lower dose of levofloxacin (250 mg twice daily) was as effective as the higher dose (500 mg twice daily).

In small trials, rifabutin has been shown to be effective in eradicating *H. pylori* in patients who have failed traditional therapies. In a randomized comparison of levofloxacin triple therapy and rifabutin triple therapy in patients who failed two other treatment trials, levofloxacin triple therapy was significantly better than rifabutin triple therapy (85% vs 45%). Side effects occurred frequently with both regimens: leukopenia with rifabutin in 25% of patients and myalgia with levofloxacin in 30% of patients.<sup>42</sup> A recent study suggested that the efficacy of rifabutin triple therapy was reduced in patients who had 2 or more prior treatment trials.<sup>43</sup>



**Figure 1.** Current treatment strategies for *Helicobacter pylori* (A–C). Some experts use rifabutin triple therapy before levofloxacin therapy.

**Two Proposed Strategies for *H. pylori* Treatment**

It is difficult for clinicians to make practical decisions with the changes that are taking place in the *H. pylori* landscape. There are two main therapeutic strategies: traditional strategy (Figure 1) and emerging strategy (Figure 2).

**Traditional Strategy**

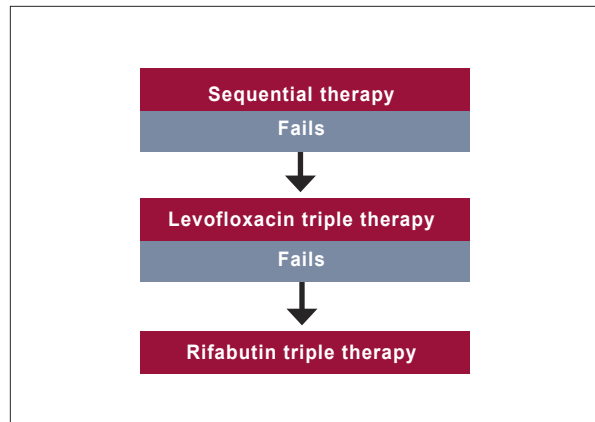
Traditional treatment strategies are based upon sound evidence and, although the success rate of individual regimens is now dissatisfactory, the use of post-treatment testing and salvage regimens usually allows for a successful cure. A practical management strategy using the treatment regimens recommended in current guidelines still appears to be effective, though a substantial number of patients require a second course of treatment.

**Emerging Strategy**

The high degree of success seen in trials with sequential therapy from different regions of the world makes this form of therapy an intriguing possibility as a new initial treatment.<sup>19</sup> There are some major gaps in our knowledge regarding this emerging form of therapy. Larger studies of treatment outcome are necessary in patients with clarithromycin resistance. There are no studies from North America. In addition, there is also no clear strategy for patients who fail sequential therapy. To date, there have been only a few failures with this form of treatment and, therefore, the accumulated experience is small. The available data suggest that these patients can be effectively treated with levofloxacin triple therapy.<sup>16</sup> Figure 2 shows an emerging strategy based upon initial treatment with

sequential therapy. It should be recognized that data are still being gathered on the treatment of failures with sequential therapy, but it is likely that levofloxacin and rifabutin will remain effective in this setting because the patients have not been exposed to these agents as part of initial therapy.

The declining rates of eradication with current treatment regimens for *H. pylori* are a cause for concern. Sequential therapy is an emerging strategy that will likely play an important role in therapy for *H. pylori* in the years to come.



**Figure 2.** Emerging sequence of therapies with sequential therapy.

## References

- Vakil N, Megraud F. Eradication therapy for *Helicobacter pylori*. *Gastroenterology*. 2007;133:985-1001.
- Duck WM, Sobel J, Pruckler JM, Song Q, Swerdlow D, et al. Antimicrobial resistance incidence and risk factors among *Helicobacter pylori*-infected persons, United States. *Emerg Infect Dis*. 2004;10:1088-1094.
- Koivisto TT, Rautelin HI, Voutilainen ME, Niemela SE, Heikkinen M, et al. Primary *Helicobacter pylori* resistance to metronidazole and clarithromycin in the Finnish population. *Aliment Pharmacol Ther*. 2004;19:1009-1017.
- Janssen MJ, Hendrikse L, de Boer SY, Bosboom R, de Boer WA, et al. *Helicobacter pylori* antibiotic resistance in a Dutch region: trends over time. *Neth J Med*. 2006;64:191-195.
- Petersen AM, Gjode P, Vinge OD, Jensen S, Krogfelt KA. *Helicobacter pylori* antimicrobial resistance and risk factors in Denmark 1998-2004: no need for concern? *Helicobacter*. 2006;11:210-211.
- Mohammadi M, Doroud D, Mohajeri N, Massarrat S. *Helicobacter pylori* antibiotic resistance in Iran. *World J Gastroenterol*. 2005;11:6009-6013.
- John Albert M, Al-Mekhaizeem K, Neil L, Dhar R, Dhar PM, et al. High prevalence and level of resistance to metronidazole, but lack of resistance to other antimicrobials in *Helicobacter pylori*, isolated from a multiracial population in Kuwait. *Aliment Pharmacol Ther*. 2006;24:1359-1366.
- Lwai-Lume L, Ogutu EO, Amayo EO, Kariuki S. Drug susceptibility pattern of *Helicobacter pylori* in patients with dyspepsia at the Kenyatta National Hospital, Nairobi. *East Afr Med J*. 2005;82:603-608.
- Cockburn J, Gibberd RW, Reid AL, Sanson-Fisher RW. Determinants of non-compliance with short term antibiotic regimens. *Br Med J (Clin Res Ed)*. 1987;295:814-818.
- Vakil N, Cutler A. Ten-day triple therapy with ranitidine bismuth citrate, amoxicillin, and clarithromycin in eradicating *Helicobacter pylori*. *Am J Gastroenterol*. 1999;94:1197-1199.
- Sherwood P, Wibawa J, Atherton J, Jordan N, Jenkins D, et al. Impact of acid secretion, gastritis and mucus thickness on gastric transfer of antibiotics in rats. *Gut*. 2002;51:490-494.
- Goddard A. Review article: factors influencing antibiotic transfer across the gastric mucosa. *Aliment Pharmacol Ther*. 1998;12:1175-1184.
- Erah P, Goddard A, Barrett D, Shaw P, Spiller R. The stability of amoxicillin, clarithromycin and metronidazole in gastric juice: relevance to the treatment of *Helicobacter pylori* infection. *J Antimicrob Chemother*. 1997;39:5-12.
- Goodwin A, Kersulyte D, Sisson G, Veldhuyzen van Zanten SJ, Berg DE, Hoffman PS. Metronidazole resistance in *Helicobacter pylori* is due to null mutations in a gene (rdxA) that encodes an oxygen-insensitive NADPH nitroreductase. *Mol Microbiol*. 1998;28:383-393.
- Mégraud F. *H. pylori* antibiotic resistance: prevalence, importance, and advances in testing. *Gut*. 2004;53:1374-1384.
- Vaira D, Zullo A, Vakil N, Gatta L, Ricci C, et al. Sequential therapy versus standard triple-drug therapy for *Helicobacter pylori* eradication: a randomized trial. *Ann Intern Med*. 2007;146:556-563.
- Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, et al. Current concepts in the management of *Helicobacter pylori* infection—The Maastricht III Consensus Report. *Gut*. 2007;56:772-781.
- Chey WD, Wong BC. Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102:1808-1825.
- Vakil N, Vaira D. Sequential therapy for *Helicobacter pylori*: time to make the switch? *JAMA*. 2008;300:1346-1347.
- Laine L, Fennerty MB, Osato M, Sugg J, Suchower L, et al. Esomeprazole-based *Helicobacter pylori* eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials. *Am J Gastroenterol*. 2000;95:3393-3398.
- Laine L, Hunt R, El-Zimaity H, Nguyen B, Osato M, Spenard J. Bismuth-based quadruple therapy using a single capsule of bismuth biscaltrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin, and clarithromycin for eradication of *Helicobacter pylori* in duodenal ulcer patients: a prospective, randomized, multicenter, North American trial. *Am J Gastroenterol*. 2003;98:562-567.
- Laine L, Suchower L, Frantz J, Connors A, Neil G. Twice-daily, 10-day triple therapy with omeprazole, amoxicillin, and clarithromycin for *Helicobacter pylori* eradication in duodenal ulcer disease: results of three multicenter, double-blind, United States trials. *Am J Gastroenterol*. 1998;93:2106-2112.
- Fennerty MB, Kovacs TO, Krause R, Haber M, Weissfeld A, et al. A comparison of 10 and 14 days of lansoprazole triple therapy for eradication of *Helicobacter pylori*. *Arch Intern Med*. 1998;158:1651-1656.
- Bochenek WJ, Peters S, Fraga PD, Wang W, Mack ME, et al. *Helicobacter pylori* Pantoprazole Eradication (HELPE) Study Group. Eradication of *Helicobacter pylori* by 7-day triple-therapy regimens combining pantoprazole with clarithromycin, metronidazole, or amoxicillin in patients with peptic ulcer disease: results of two double-blind, randomized studies. *Helicobacter*. 2003;8:626-642.
- Vakil N, Lanza F, Schwartz H, Barth J. Seven-day therapy for *Helicobacter pylori* in the United States. *Aliment Pharmacol Ther*. 2004;20:99-107.
- Graham D, Yamaoka Y. Ethical considerations of comparing sequential and traditional anti-*Helicobacter* therapy. *Ann Intern Med*. 2007;147:434-435.
- Sharma VK, Howden CW. A national survey of primary care physicians' perceptions and practices related to *Helicobacter pylori* infection. *J Clin Gastroenterol*. 2004;38:326-331.
- Delaney BC, Qume M, Moayyedi P, Logan RF, Ford AC, et al. *Helicobacter pylori* test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial). *BMJ*. 2008;336:651-654.
- Rokkas T, Sechopoulos P, Robotis I, Margantinis G, Pistiolas D. Cumulative *H. pylori* eradication rates in clinical practice by adopting first and second line regimens proposed by the Maastricht III consensus conference and a third line empirical regimen. *Am J Gastroenterol*. 2008 Sep 4; [Epub ahead of print].
- Gisbert JP, Gisbert JL, Marcos S, Jimenez-Alonso I, Moreno-Otero R, Pajares JM. Empirical rescue therapy after *Helicobacter pylori* treatment failure: a single-centre study of 500 patients. *Aliment Pharmacol Ther*. 2008;27:346-354.
- Katellaris PH, Forbes GM, Talley NJ, Crotty B. A randomized comparison of quadruple and triple therapies for *Helicobacter pylori* eradication: The QUAD-RATE Study. *Gastroenterology*. 2002;123:1763-1769.
- Calvet X, Ducons J, Guardiola J, Tito L, Andreu V, et al. Group for Eradication Studies from Catalonia and Aragon (Gresca). One-week triple vs quadruple therapy for *Helicobacter pylori* infection—a randomized trial. *Aliment Pharmacol Ther*. 2002;16:1261-1267.
- O'Morain C, Borody T, Farley A, De Boer WA, Dallaire C, et al. International multicentre study. Efficacy and safety of single-triple capsules of bismuth biscaltrate, metronidazole and tetracycline, given with omeprazole, for the eradication of *Helicobacter pylori*: an international multicentre study. *Aliment Pharmacol Ther*. 2003;17:415-420.
- Gene E, Calvet X, Azagra R, Gisbert J. Triple vs. quadruple therapy for treating *Helicobacter pylori* infection: a meta-analysis. *Aliment Pharmacol Ther*. 2003;17:1137-1143.
- Treiber G, Wittig J, Ammon S, Walker S, van Doorn LJ, Klotz U. Clinical outcome and influencing factors of a new short-term quadruple therapy for *Helicobacter pylori* eradication: a randomized controlled trial (MACLOR study). *Arch Intern Med*. 2002;162:153-160.
- Rinaldi V, Zullo A, Pugliano F, Valente C, Diana F, Attili AF. The management of failed dual or triple therapy for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther*. 1997;11:929-933.
- Jafri N, Hormung C, Howden C. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naïve to treatment. *Ann Intern Med*. 2008;148:1-9.
- Gatta L, Di Mario F, Zullo A, Vaira D. Errors in a meta-analysis of treatments for *Helicobacter pylori* infection. *Ann Intern Med*. 2008;149:686.
- Delgado J, Bujanda L, Gisbert P, Tito L, Calvet X, Castro M. Effectiveness of a 10-day sequential treatment for *Helicobacter pylori* eradication in clinical practice. *Am J Gastroenterol*. 2008;103:2220-2223.
- Wu D, Hsu P, Wu J, Opekun A, Graham D. Randomized controlled comparison of sequential and quadruple therapies for *H. pylori* infection. *Gastroenterology*. 2008;134:A24.
- Saad RJ, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent *Helicobacter pylori* infection: a meta-analysis. *Am J Gastroenterol*. 2006;101:488-496.
- Gisbert JP, Gisbert JL, Marcos S, Moreno-Otero R, Pajares JM. Third-line rescue therapy with levofloxacin is more effective than rifabutin rescue regimen after two *Helicobacter pylori* treatment failures. *Aliment Pharmacol Ther*. 2006;24:1469-1474.
- Van der Poorten D, Katellaris PH. The effectiveness of rifabutin triple therapy for patients with difficult-to-eradicate *Helicobacter pylori* in clinical practice. *Aliment Pharmacol Ther*. 2007;26:1537-1542.