How to Treat *Heliobacter pylori* First-Line, Second-Line, and Future Therapies

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How to Treat *Heliobacter pylori*
First-Line, Second-Line, and Future Therapies

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Similar to any bacterial infection, the treatment of *Helicobacter pylori* infection is based on the use of antimicrobial agents. The first experiments performed during the early years after the discovery of *H. pylori* showed that no single agent could achieve its eradication at a sufficient rate. Dual antibiotic therapy increases the cure rate and avoids the selection of resistant strains. Despite these improvements, however, dual treatment was not efficient enough to be recommended for routine treatment.

An adjuvant therapy is needed, and until now the best adjuvant therapy has comprised drugs that increase the pH of the stomach (i.e., antisecretory drugs and especially proton-pump inhibitors [PPI]) because most antibiotics have a decreased activity at low pH. [43] Three antibiotics have drawn special attention: (1) Clarithromycin, the best compound in the macrolide group, but it is costly and selects resistant strains; (2) amoxicillin, for which resistance is virtually absent, but it has a poor diffusion in gastric tissue; and (3) metronidazole, which has an excellent diffusion, but it induces and selects resistant strains. Because of these drawbacks, the success of the first-line therapies in practice is limited to 70% to 80%. Research now is focused on second-line therapies comprising a combination of other antibiotics with those previously cited; there is a need for new compounds specific for *H. pylori*, which should constitute future therapies.

FIRST-LINE THERAPY

High-Cost Treatments

Proton-Pump Inhibitor-Based Triple Therapies

The concept of PPI-based triple therapy was introduced in the early 1990s, at a time when the current dual therapy of omeprazole and amoxicillin, which had produced promising results, showed a lack of reproducibility in certain settings. The first PPI-based triple therapy to be administered was omeprazole and amoxicillin with metronidazole given for 10 days.[36] A new macrolide, clarithromycin, which had shown significant efficacy against *H. pylori* in the absence of antisecretory drugs,[25] was considered for the triple therapy. In Bologna, Bazzoli et al[5] proposed triple therapy using a low dose of clarithromycin (250 mg twice a day) and a low dose of omeprazole (20 mg every other day) with metronidazole for 7 days. These investigators achieved a high rate of eradication, reaching 100% when they first presented their data.

In Bordeaux, another approach was developed to take into account the high rate of *H. pylori* resistance to metronidazole. The logic was to replace metronidazole with amoxicillin, to which no resistance was then reported; to give higher doses of clarithromycin (500 mg twice a day); and to treat the patient for 10 days. The first clinical trial by Lamouliatte et al[37] was highly successful.

These two regimens--called the Italian and French, Bologna and Bordeaux, or Bazzoli and Lamouliatte regimens--are still used mainly with some variation in terms of dosage and length of treatment, and they have superceded the first PPI triple therapy containing amoxicillin and metronidazole. Numerous studies have been performed since 1993 and have produced an impressive database. This article does not consider all the studies but emphasizes the large multicenter studies performed with different PPIs as well as the pool analysis performed by Unge[70] and the meta-analysis performed by Laheij et al.[30] The PPI-based therapies described here as well as the ranitidine bismuth citrate (RBC)-based triple therapies described later have been recommended in different consensus conferences around the world.[15] [32] [69]

The MACH1 study was the first large multicenter study carried out in Northern Europe comparing several triple therapies with different doses of clarithromycin. The findings confirmed that it was valid to use 250 mg twice a day in the Bazzoli therapy and 500 mg twice a day in the Lamouliatte therapy. All of these regimens were given for 7 days and with a double dose of omeprazole.[40] A similar study was performed in the United Kingdom using lansoprazole (30 mg twice a day) instead of omeprazole (20 mg twice a day), and equally satisfactory results were obtained.[52] Similar results were obtained in Germany when pantoprazole (40 mg twice a day) was used with clarithromycin and metronidazole.[16]

The meta-analysis of Laheij et al[30] gives the best value of cure rates that can be obtained because (1) it takes into account all of the published data, (2) the heterogeneity between the studies is modeled by means of an ordinary least-squares regression equation, and (3) the heterogeneity in the precision of the cure rates caused by different study sizes is corrected by applying a weighted regression analysis. The drawback is the inclusion of nonrandomized clinical trials, which may confound the results; however, no statistically significant difference was found between randomized and nonrandomized trials. The inclusion of some abstracts that may carry incomplete data may be criticized. The results according to per protocol or intention to treat are presented in Table 1 . The three therapies had a similar efficacy (<5% difference) with the ranking PPI-clarithromycin-metronidazole greater than PPI-amoxicillin-clarithromycin greater than PPI-amoxicillin-metronidazole. The small differences between the per-protocol and intention-to-treat results are a first indication that the patients do not suffer much from side effects, which would lead them to stop the treatment.

TABLE 1 -- ADJUSTED CURE RATES OF PROTON-PUMP INHIBITOR TRIPLE THERAPIES AND QUAD META-ANALYSIS

	Per Protocol		Inter
Drugs Administered	***No. Studies***	**% *Cure***	***No. Studies***
PPI, amoxicillin, nitroimidazole	82	82.4	50
PPI, amoxicillin, clarithromycin	77	86.1	48
PPI, clarithromycin, nitroimidazole	122	87.1	80
RBC, amoxicillin, clarithromycin	6	87.6	3
RBC, clarithromycin,	7	90.7	7

nitroimidazole			
Standard triple therapy*	64	79.1	42
Quadruple therapy* (with PPI)	26	90.6	24
Quadruple therapy* (with anti-H_2)	11	89	8

Including tetracycline.

PPI = Proton-pump inhibitor; RBC = ranitidine bismuth citrate.

Data from Laheij RJF, van Rossum LGM, Jansen JBMJ, et al: Evaluation of treatment regimens to cure Helicc analysis. Aliment Pharmacol Ther 13:857-864, 1999.

Factors Influencing Outcome.

Because the overall efficacy is incomplete, one may wonder what the causes of failure are.

Factors Linked to Treatment Used

Dose of clarithromycin.

In the meta-analysis, increasing the dose of clarithromycin to 1.5 g significantly improved the cure rate, and this was true for regimens containing clarithromycin and PPI. The difference was greatest for the combination with amoxicillin. Clinical experience using low doses of clarithromycin is especially poor.[34] In contrast, the doses of amoxicillin and metronidazole do not seem to influence the outcome.

Duration of Treatment.

The optimal duration of treatment remains controversial. In Europe, after the MACH studies and other multicenter studies carried out in the northern part of the continent, recommendations were made in the Maastricht Consensus Report[20A] as well as in consensus statements from different countries to treat patients for 7 days; the corresponding regimens were approved by the respective regulatory authorities. The only exception to this practice is in the United States, where 14-day courses were advocated and subsequently approved by the Food and Drug Administration (FDA).

In the meta-analysis of Laheij et al,[30] treatment duration did not influence the cure rate. Two reports from the United States show an improvement when the treatment including amoxicillin and clarithromycin is given for a longer time: 14 days greater than 10 days greater than 7 days.[31] In France, Lamouliatte et al[38] compared regimens of lansoprazole, amoxicillin, and clarithromycin given for 7 and 10 days and found a significant difference favoring a 10-day duration.

Type and Dose of Proton-Pump Inhibitor.

The pooled analysis of Unge[70] is presented according to the type of PPI used, in contrast to the analysis of Laheij et al.[30] Among the three combinations, there seems to be a trend for a higher efficacy of omeprazole over pantoprazole and lansoprazole, but the difference is not significant. Increasing the dose of PPI does not seem to improve the cure rate. A high dose of PPI is more important when the amoxicillin and clarithromycin combination is used. When no PPI was administered, these two antibiotics led to only a 25% cure rate in the MACH2 study versus 46% for clarithromycin and metronidazole.[39]

Factors Linked to the Strains

Resistance of Helicobacter pylori to Antimicrobial Agents.

The impact of resistance on the clinical outcome of treatment is different for metronidazole and clarithromycin.[47] For metronidazole, despite the presence of resistant strains, a cure rate of 75% can be achieved (i.e., a decrease of 20% compared with the rate observed for susceptible strains).[39] In developed countries, the resistance is no greater than 50%. The impact on the overall success does not exceed a 10% decrease in the

cure rate for the PPI, clarithromycin, and metronidazole regimens. The impact is greater when clarithromycin is replaced by amoxicillin.[26] The low rate of metronidazole resistance observed in northern Italy[6] may explain why the Bazzoli therapy is so successful in Bologna.

In contrast, the impact of clarithromycin resistance is much more important. The cure rate ranges from 0[35] to 50%.[74] The rate of resistance to macrolides still is low, usually ranging from 0 to 15%, with 8% in the United States,[73] 14% in France,[11] but only 2% in Sweden.[39] Only reports comprising large numbers of cases that are representative of the population and lead to narrow confidence intervals should be considered.[44] The impact of this resistance on the overall cure rate varies from a 7% to 15% decrease. If strains are resistant to clarithromycin and metronidazole, however, no eradication can be achieved.

A report was published on an *H. pylori* strain that was resistant to amoxicillin (minimal inhibitory concentration >8 mg/L) and isolated from a patient having received several courses of amoxicillin for a respiratory tract infection.[72] This resistance mechanism has been linked to a mutation on the penicillinbinding protein 1A.[29] Dore et al[20] claim to have isolated amoxicillin-tolerant strains in Sardinia, and the mechanism could be the lack of a certain penicillin-binding protein (penicillin-binding protein [PBP-D]). Strains with a decreased susceptibility to amoxicillin (0.25 or 0.5 mg/L) also have been reported. The impact of these findings on the cure rate is unknown.

Strain Type.

A wide variety of *H. pylori* strains exists. Some strains harboring a pathogenicity island (*cag* PAI) are associated with more severe diseases. Such strains could behave differently with regard to eradication treatment. It has been shown that strains from patients with peptic ulcer disease are easier to eradicate than strains from patients with nonulcer dyspepsia.[27] [71]

The authors conducted a multivariate analysis of the risk factors for treatment failure in a large multicenter study involving patients with nonulcer dyspepsia. A heterogeneity was observed with regard to *cag* status, which was found to be a significant risk factor for failure. This heterogeneity can be explained partially by the increased inflammation generated and possibly by the higher growth rate, two factors that favor the diffusion and action of the antibiotics.[12]

Factors Linked to the Patient.

In the meta-analysis of Laheij et al,[30] the only important factor associated with differences in cure rates, beside the medication combination, was the country in which the trial took place. Other factors, including smoking, alcohol consumption, and diet as well as the type of strain and the level of resistance to antibiotics, may vary from country to country. Compliance also may be different, geographically speaking, for example, in Europe between Nordic and Mediterranean countries. The side effects of the regimen can influence the compliance. Side effects are in the range of 5% to 20% for the three regimens described, however, and cannot be the reason for this difference.

Ranitidine Bismuth Citrate-Based Triple Therapies

RBC was developed as a specific drug for the treatment of *H. pylori* infection. The concept was to associate the well-recognized antisecretory properties of ranitidine with those of bismuth salts (i.e., anti-*H. pylori* activity and mucoprotective properties).[68] Although there always has been a controversy about whether to consider RBC as a unique entity or as an association of two drugs, it is administered as a unique drug and has a practical interest.

RBC per se cannot cure *H. pylori* infection. It must be used in association with antibiotics. The first combination used and approved in the United States was RBC and clarithromycin given for 2 weeks.[61] Many studies have since been performed with this dual therapy as well as using a combination of two antibiotics with RBC.

The same antibiotics as those combined with PPI essentially have been used: clarithromycin and amoxicillin or clarithromycin and nitroimidazole (metronidazole), usually for 1 week. Laheij et al[30] found an adjusted cure rate according to per-protocol and intention-to-treat analysis for the combination clarithromycin and amoxicillin of 87.6% and 81.2% and for the combination clarithromycin and nitroimidazole of 90.7% and

78.3%.[30] Susceptibility data are available in only a few of these studies, and it is not possible to conclude that the good efficacy is due to the effect on resistant strains, although this may be the case.[22] [62]

In a dual-therapy study, RBC and clarithromycin eradicated *H. pylori*, in contrast to omeprazole and clarithromycin, despite the resistance of the organism to clarithromycin.[46] In vitro data favor the existence of a synergy between RBC and clarithromycin.[42] [51] [55] The combination of RBC, amoxicillin, and tinidazole was used in only one study[65] with a limited efficacy (61% cure rate).

Low-Cost Treatments

The treatments previously described are satisfactory in terms of efficacy and safety, but their high cost is a major drawback, essentially resulting from the price of PPI, RBC, and clarithromycin. Given that most people infected with *H. pylori* are living in developing countries where the amount of money that can be spent on health care is extremely limited, it is important to consider low-cost treatments. In this respect, the standard triple therapy using bismuth salts and other bismuth-based therapies should be recommended.[17]

Standard Triple Therapy

Standard triple treatment was the first effective treatment to be proposed in 1987[10] and subsequently recommended by a Working Party held at the World Congresses of Gastroenterology in Sydney in 1990.[2] A review by Penston[58] in 1994 included 67 studies and 3287 patients. The global eradication rate was 82% by per-protocol and 72% by intention-to-treat analyses.

The scheme using bismuth, amoxicillin, and nitroimidazole was less effective than that of bismuth, tetracycline, and nitroimidazole with eradication rates of 75% and 87%, respectively. Since 1994, this triple therapy has been superceded by PPI-based and RBC-based triple therapies in developed countries as first-line treatment, but it remains an important option in developing countries because of its relatively low cost.

Factors Influencing Outcome Linked to the Treatment Regimen.

Besides the type of antibiotic used (amoxicillin or tetracycline) as previously mentioned, the duration of the treatment has been tested. No significant difference was found between 1 week, 2 weeks, or more than 2 weeks for both regimens. A treatment given for less than 1 week was significantly less effective. The type of bismuth salt used, mainly colloidal bismuth subcitrate or bismuth subsalicylate, does not seem to influence the outcome.

Major limitations of this treatment are the necessity to take the drugs 4 times a day and the borderline tolerance because of side effects. Penston[58] reported that side effects, including diarrhea, nausea, and a bad taste in the mouth, occurred in 32% of cases and led to stopping the treatment in 4% of patients.

Factors Influencing Outcome Linked to the Strain.

Currently, tetracycline resistance has been reported in only one strain,[50] and amoxicillin resistance, which has been discussed previously, is limited, if it exists at all. Nitroimidazole resistance is common, especially in tropical countries, where these compounds are used to treat parasitic infections. For example, in six studies in which triple therapies were used for at least 1 week, the eradication rate decreased from 93% (186 of 200 patients) to 40% (44 of 110 patients)[45] in case of resistance to metronidazole. At this stage, no study on the impact of other strain characteristics (e.g., *cag* status) has been performed.

Factors Influencing Outcome Linked to the Patient.

Because of the need for 4 daily doses of the drugs, this treatment is not convenient, and compliance usually is unsatisfactory. Graham et al[24] showed that taking less than 65% of the drugs led to a significant decrease in efficacy. No other factors have been shown to have an impact.

Other Bismuth-Based Triple Therapies

Because of the possible inefficacy of standard triple therapies and especially the impact of metronidazole

resistance, other antibiotics have been used. One of the most interesting is furazolidone because *H. pylori* has not yet been found to be resistant to this drug. This compound belongs to the nitrofurane group. It was originally used to treat *H. pylori* infection in China.[75] Trials have been conducted in South America, especially in Brazil, Colombia, and Peru. Furazolidone was used instead of metronidazole in the standard triple therapy with amoxicillin in 1994[21] and with tetracycline in 1996.[56] In the pilot study of Segura et al,[67] 30 patients were treated with bismuth subcitrate (240 mg twice a day), furazolidone (100 mg daily), and amoxicillin (500 mg daily) for 14 days. Of patients, 86% were cured (95% confidence interval, 65 to 94). All patients completed the study, and the side effects were mild. A similar study was performed in Peru, the difference being that all drugs were given 3 times a day and the bismuth salt was bismuth subsalicylate instead of subcitrate. The eradication rate was 82%, higher than in the arm in which metronidazole was used instead of furazolidone (56%) (P = 0.015).[63]

de Idiaquez et al[19] performed a study replacing amoxicillin with tetracycline. The investigators used 4-times-daily dosage but for only 10 days. The per-protocol eradication rate was 91.5% (54 of 59). Other trials using furazolidone also have been performed, but their treatment did not fit the criterion of low cost because they included a PPI and clarithromycin.[41] The bismuth-based and furazolidone-based triple therapies were recommended as first-line therapies at the Latin American Consensus Conference held in February 1999.[13]

SECOND-LINE THERAPY

Pragmatic Approach

The pragmatic approach that most gastroenterologists favor is the use of a quadruple therapy when the first treatment has not been successful. This quadruple therapy consists of the standard triple therapy (including tetracycline) plus a PPI.[9] Quadruple therapy was found to be effective in the first trials performed in the Netherlands, Hong Kong, and Australia and led to an eradication rate of 90% or more regardless of the status of metronidazole resistance. The use of an H_2 -receptor antagonist gives an equivalent result.

In the meta-analysis of Laheij et al[30] according to intention to treat and per protocol, the eradication rate with a PPI (26 studies) was 90.6% and 81.7%, respectively, and with an H_2 -receptor antagonist (11 studies) was 89% and 79.6%, respectively. This was the only therapy for which metronidazole resistance did not seem to have any influence. The duration of treatment can be limited to 1 week; an additional week does not improve the result and leads to substantial side effects.[18] The compliance to this complicated therapy should be improved when three of the drugs are available in a single pill.

Other Approaches Using Triple Therapies

Given that in developed countries the most commonly used treatment includes clarithromycin and that the selection of resistance to this compound is a major risk factor for failure, it is important in the case of failure to find an alternative to clarithromycin. Publications are limited in this field. A combination of PPI, amoxicillin, and metronidazole could be used. Data from the HOMER study in which different doses of metronidazole were given indicated a trend toward a better efficacy using the highest dose on resistant strains, but the difference was not statistically significant.[3] It also seems realistic under such circumstances to increase the length of treatment from 1 to 2 weeks. This combination currently is being tested in France in a prospective study on eradication failure. The rationale is that the concentration of drug in the mucosa is dose dependent[23] and that there is a continuum of minimal inhibitory concentrations and not a big gap between susceptibility and resistance.[48]

Resistance to fluoroquinolones is low in most countries (e.g., 3.4% in France[7]), and these compounds, the most effective being ciprofloxacin, are potential candidates for second-line treatment. The results have not reached clinicians' expectations, however. Only 25% of the patients were cured with ciprofloxacin (750 mg twice a day), amoxicillin (1 g twice a day), and omeprazole (20 g twice a day).[33] Poor results were obtained when tetracycline was given with amoxicillin in PPI-based or RBC-based triple therapies (eradication rate, 20% to 35%),[59] whereas tetracycline given with metronidazole led to a 91% eradication rate when it was combined with omeprazole.[64] The cure rate was 80% with RBC.[4] All treatments lasted 7 days. However, Cudia et al[14] cured 17 of 19 patients (89.5%) when minocycline (100 mg twice a day) was given with amoxicillin (1 g twice a day) and RBC (400 mg twice a day) (Table 2) .

TABLE 2 -- ALTERNATIVE TRIPLE THERAPIES WITH PROTON-PUMP INHIBITOR OR RANITIDINE BIS
CORRESPONDING ERADICATION RATES

Drugs Administered	Treatment Duration (d)	Eradication Rate (%)	95% CI
PPI, amoxicillin, metronidazole	7	83	75-89
PPI, tetracycline, metronidazole	7	91	85-96
PPI, rifabutin, amoxicillin *	10	79	64-94
PPI, ciprofloxacin, amoxicillin *	7	25	7-52
PPI, tetracycline, amoxicillin	7	35	25-45
RBC, tetracycline, tinidazole *	14	82	75-97
RBC, tetracycline, metronidazole	7	80	67-90
RBC, minocycline, amoxicillin *	14	90	67-98
RBC, tetracycline, amoxicillin	7	20	12-29

CI = Confidence interval; PPI = proton-pump inhibitor; RBC = ranitidine bismuth citrate.

*Tested after failure of a PPI triple therapy.

Furazolidone, the other compound for which no resistance has been found, currently is unavailable in most developed countries and cannot be an alternative. Rifampins are compounds for which resistance is seldom detected in *H. pylori*. Perri et al [60] proposed a *rescue* therapy consisting of rifabutin (300 mg every day) given with amoxicillin (1 g twice a day) and pantoprazole (40 mg twice a day) for 10 days. Perri et al [60] cured 79% (95% confidence interval, 64 to 94) of 29 patients treated, and only 4% experienced side effects. A similar regimen was used by Bock et al [8] in which rifabutin was given twice a day for 10 days. These investigators achieved an eradication rate of 85% (17 of 20) despite the fact that these patients previously had received three eradication treatments. No resistance to rifabutin was observed.

One of the few trials dealing with retreatment after failure of a PPI-based triple therapy (PPI, clarithromycin, and amoxicillin) used RBC, tetracycline and tinidazole for 2 weeks. The results were good (intention-to-treat, 82%; per protocol 86%) and slightly better than the results of the first-line treatment. The susceptibility data are not available to evaluate the impact on resistant strains. [66] The same regimen was used by Monkemuller and Hirschowitz [53] as a first-line treatment with similar success.

Dual Therapy with Proton Pump Inhibitor and Amoxicillin

PPI and amoxicillin dual therapy was the preferred therapy at the beginning of the 1990s. It was abandoned because of the inconsistent results obtained, which were globally inferior to those of PPI-based triple therapies. The reason probably is linked to the pharmacokinetic properties of the compound. In contrast to macrolides, amoxicillin is a strictly extracellular antibiotic (i.e., it diffuses into the gastric mucosa only when it is present in the bloodstream). In contrast to metronidazole, amoxicillin never reaches important concentrations in the gastric mucosa. This compound is interesting because of the apparent absence of resistance in *H. pylori*, which is currently being debated.

A way of solving the pharmacologic problem is to administer amoxicillin parenterally to have a high and constant flow of the compound at the mucosal level that would be sufficient to kill the bacteria. Such a treatment has been performed in a pilot study and has led to satisfactory results. [1] This alternative is not convenient and cannot be used widely. It could be a solution when one is dealing with a serious disease in

which the eradication of *H. pylori* is desirable but not achievable by other treatments. An alternative is to give an oral treatment at a high dosage (e.g., omeprazole [40 mg 3 times a day] and amoxicillin [1 g 3 times a day] for 2 weeks). Peitz et al [57] reported an 80% cure rate when they applied this regimen to previous failure cases as well as Jaup, [28] who used only 750 mg of amoxicillin 3 times a day.

FUTURE THERAPIES

Many new compounds currently are being evaluated, including macrolides other than clarithromycin (e.g., azithromycin and roxithromycin). The minimal inhibitory concentration of these compounds on *H. pylori* are inferior to that of clarithromycin. If the right dose and combination can be found, however, it is possible that a satisfactory result could be obtained. In the authors' opinion, the drugs that will emerge in the future most likely will be nitazoxanide, possibly a compound from the ketolide family, and molecules issued from research on genomics. The authors are doubtful about the emergence of treatments based on other concepts such as antiadherent molecules or hyperimmune colostrum. [54]

Nitazoxanide

Nitazoxanide is a nitrothiazolamide compound that shares many properties with the nitroimidazoles. It has the advantage of being well tolerated, however, and it does not select *H. pylori*-resistant strains. In vitro the minimal inhibitory concentrations are close to those of strains susceptible to metronidazole. No resistance has been detected after subsequent passages on agar containing subinhibitory concentrations of nitazoxanide or after failure of a nitazoxanide treatment. In a dose-ranging trial of nitazoxanide with omeprazole, an eradication rate of 83% per protocol was obtained. [49] Large trials are being conducted to confirm these results.

Ketolides

Ketolides are derived from the macrolide group of antibiotics. They have been developed to be active against macrolide-resistant bacteria. Some ketolides are active against macrolide-resistant *H. pylori*, but their minimal inhibitory concentration on susceptible strains is not as good as that of clarithromycin. Trials to test their effectiveness against *H. pylori* have not been conducted.

New Drugs Based on Genomics

New compounds active against *H. pylori* may emerge from well-known families of antibiotics, such as beta-lactams and fluoroquinolones, or from new antibiotic groups discovered using the classic approach. The complete genomic sequencing of two *H. pylori* strains has created a new way of finding active drugs, which specifically target certain vital functions of the bacterium. Numerous genes are specific for *H. pylori* and common to all *H. pylori* strains. Postgenomic methods, especially using DNA chips, allow an effective screening of these genes. Once their vital role is confirmed by mutagenesis, they can be screened easily against thousands of small chemical molecules using high-throughput technology. This is the beginning of the process of drug discovery in this new era.

SUMMARY

Numerous trials have been performed during the 1990s to define the optimal therapy for *H. pylori* infections. The proposed PPI-based and RBC-based triple therapies lead to satisfactory results. Their first drawback is their cost, and for this reason, many infected people who need treatment worldwide cannot benefit from these regimens. Combinations including bismuth salts and furazolidone, although less convenient and inducing more side effects, can achieve the same goal, however.

Failures of first-line therapies essentially are due to antimicrobial resistance, which increases with the selection pressure resulting from the use of these drugs. Second-line treatments using antimicrobial agents for which *H. pylori* resistance is low or nonexistent are being tested to find alternatives to the quadruple

therapy. Ciprofloxacin or tetracycline administered with amoxicillin and a PPI has not achieved this goal, in contrast to rifabutin. Combinations including metronidazole with amoxicillin and PPI or with tetracycline and RBC also are potential solutions. There is a need for new drugs, which should be highly effective, nonselective of resistant strains, and without side effects, to improve current regimens. These drugs may be the results of postgenomic studies.

Recommendations

In case of failure with a metronidazole-based regimen, the clinician should increase the dose of metronidazole and the length of the second-line treatment.

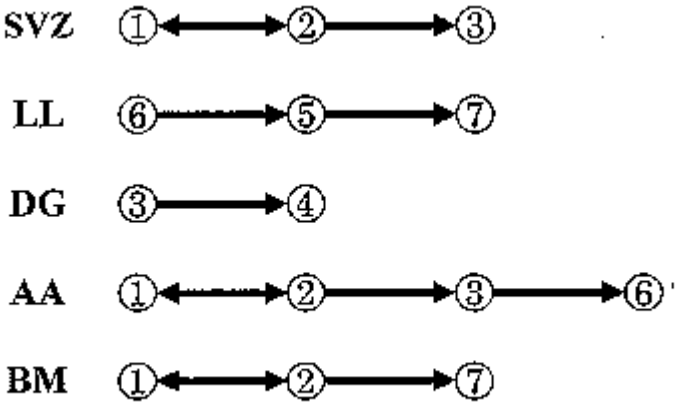
In case of failure with a clarithromycin-based regimen, this antibiotic should not be used in the second-line treatment.

Antimicrobial susceptibility testing should be monitored in specialized centers. Ideally, this testing should be performed after failure of a first-line treatment and imperatively after failure with a second-line treatment.

A second-line treatment must be given for a longer period than a first-line treatment.

Personal Recommendations

Before completing this article, the authors collected personal preferences for retreatment from several experienced clinicians. These were Sander Veldhuyzen van Zanten, MD, PhD (Queen Elizabeth Hospital, Halifax, Canada), Loren Laine, MD (University of Southern California, Los Angeles, CA), David Graham, MD (Veteran's Affairs Medical Center, Houston, TX), and Anthony Axon, MD (General Infirmary, Leeds, UK). Their suggestions corresponded to the recommendations in this article and are summarized in Figure 1 . Before embarking on such retreatment, a patient is presumed to have failed one or (more usually) two initial therapies with omeprazole, amoxicillin, clarithromycin, or RBC.



① = P-A-C	
② = P-M-C	
③ = O-B-M-T	
④ = O-B-F-T	
⑤ = P-A-R	
⑥ = P3-A3	
⑦ = P3-A3-CF	

A	=	amoxicillin 1gm BID
A3	=	amoxicillin 1gm TID
M	=	metronidazole 500mg TID
C	=	clarithromycin 500mg BID
P	=	any PPI (omeprazole 20mg BID or equivalent)
P3	=	triple dose PPI (omeprazole 40mg TID or equivalent)
R	=	rifabutin 300mg BID (original letter in nejm?)
F	=	furazolidone 100mg QID
CF	=	ciprofloxacin 500mg BID
B	=	bismuth citrate 120mg QID (De Nol) or bismuth subsalicylate 250mg QID (2 Pepto Bismol tablets QID)

Figure 1. Preferences for retreatment of *Helicobacter pylori*. BID = twice daily; TID = thrice daily; QID = four times daily; PPI = proton-pump

inhibitor.

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