Clinical Gastroenterology and Hepatology 2014;12:177–186

PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Rational *Helicobacter pylori* Therapy: Evidence-Based Medicine Rather Than Medicine-Based Evidence

David Y. Graham,[*] Yi–Chia Lee,[‡] and Ming–Shiang Wu[‡]

[*]Department of Medicine, Michael E. DeBakey VA Medical Center, and Baylor College of Medicine, Houston, Texas;
[‡]Department of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan

This article has an accompanying continuing medical education activity on page e13. Learning Objective—At the end of this activity, the successful learner will be able to reliably interpret the available data regarding therapies for *H pylori* infection, to be able to identify the regimen(s) suitable for empiric use in a region, as well as how modify those choices to identify the regimen for a specific patient that has the greatest chance of achieving a cure.

Data are available such that choice of *Helicobacter pylori* therapy for an individual patient can be reliably predicted. Here, treatment success is defined as a cure rate of 90% or greater. Treatment outcome in a population or a patient can be calculated based on the effectiveness of a regimen for infections with susceptible and with resistant strains coupled with the knowledge of the prevalence of resistance (ie, based on formal measurement, clinical experience, or both). We provide the formula for predicting outcome and we illustrate the calculations. Because clarithromycin-containing triple therapy and 10-day sequential therapy are now only effective in special populations, they are considered obsolete; neither should continue to be used as empiric therapies (ie, 7- and 14-day triple therapies fail when clarithromycin resistance exceeds 5% and 15%, respectively, and 10-day sequential therapy fails when metronidazole resistance exceeds 20%). Therapy should be individualized based on prior history and whether the patient is in a high-risk group for resistance. The preferred choices for Western countries are 14-day concomitant therapy, 14-day bismuth quadruple therapy, and 14-day hybrid sequential-concomitant therapy. We also provide details regarding the successful use of fluoroquinolone-, rifabutin-, and furazolidone-containing therapies. Finally, we provide recommendations for the efficient development (ie, identification and optimization) of new regimens, as well as how to prevent or minimize failures. The trial-and-error approach for identifying and testing regimens frequently resulted in poor treatment success. The described approach allows outcome to be predicted and should simplify treatment and drug development.

Keywords: Helicobacter pylori; Treatment; Quadruple Therapy; Review; Treatment Success; Concomitant Therapy; Sequential Therapy; Bismuth; Clarithromycin; Tetracycline; Metronidazole; Amoxicillin; Proton Pump Inhibitors; Evidence Based.

Similar to other infectious diseases, the factors responsible for effective antimicrobial therapy of a *Helicobacter pylori* infection as well as those responsible for treatment failure are both straightforward and easily discoverable. Poorly designed or executed regimens rarely produce good results. Treatment success depends on the details of the regimen including choice of drugs, doses, formulations, duration of therapy, administration in relation to meals, number of administrations/day, the use of adjuvants such as antisecretory drugs or mucolytics, and so forth.[1] Results can be defined in terms of treatment success.[2,3] For exploratory studies the primary outcome generally is expressed per protocol (PP), which controls for compliance and other variables and thus provides an indication of the potential maximum success of the regimen in clinical practice.[1] For the information to be useful and to be used to predict success in other groups, regions, and populations, the results also should be provided as the outcomes with both susceptible and resistant strains (see later). In addition, the data also should be expressed as both modified intention to treat (MITT) (which is the outcome of all who received a dose and for whom an outcome measure is available), and as intention to treat (ITT), in which those lost to follow-up evaluation typically are scored as treatment failures. ITT and MITT provide estimates of a regimen's actual success in clinical practice. PP and MITT are the most useful for the development of new regimens, whereas for large multicenter randomized comparisons most authorities prefer ITT.[4]

Considering that *H pylori* is a common infectious disease and 100% success is obtainable, outcome (eg, PP or ITT) also is scored in terms of efficacy (ie, as excellent, good, borderline acceptable, or unacceptable) because efficacy is the most important measure for patient care. For evaluating new therapies we score success (PP with susceptible strains) as excellent ($\geq$95% success), good ($\geq$90 success), borderline acceptable (85%–89% success), or unacceptable ($<$85% success). The most common causes for reliably good or excellent regimens to fail

Abbreviations used in this paper: ITT, intention to treat; MITT, modified intention to treat; PP, per protocol; PPI, proton pump inhibitor.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2013.05.028

are the presence of organisms resistant to one or more of the antimicrobials used, poor compliance with therapy, or both. A number of studies have suggested a variety of miscellaneous factors that might be important including age, presentation (eg, nonulcer dyspepsia vs duodenal ulcer), and CagA status.[5–7] However, these candidates typically have been discovered in data-dredging studies in which resistance was not assessed, and most of the studies lacked biologic plausibility. Although some of these factors (eg, nonulcer dyspepsia vs duodenal ulcer) have proven to be surrogates for differences in the prevalence of resistant strains,[8,9] none of the clinical correlates other than resistance and compliance has proven to be important in studies in which compliance and resistance have been assessed.

Therapy Choice

Similar to other infectious diseases, treatment results are best when reliably excellent regimens are used to treat patients with organisms susceptible to the antimicrobials chosen. Pretreatment susceptibility testing, either by culture of the organism or indirectly by molecular testing of stools of infected patients or fluorescent in-situ hybridization using paraffin-embedded gastric biopsy specimens, allows one to select a regimen tailored by antimicrobial susceptibility (ie, tailored therapy).[3] However, in many instances, one must choose therapy empirically and, in this instance, the best approach is to use regimens that have been proven to be reliably excellent locally.[2] That choice should take advantage of knowledge of resistance patterns obtained from local or regional antimicrobial surveillance programs and/or based on local clinical experience with regard to which regimens are effective locally. Finally, the history of the patient's prior antibiotic use and any prior therapies will help identify which antibiotics are likely to be successful and those for which resistance is probable (Figure 1).

All other things being equal, data from any area or region regarding the effects of resistance on outcome can be used reliably to predict outcome in any other area. Thus, strains with similar patterns of resistance in Italy, the United States, Iran, China, and so forth should be expected to respond alike such that, if one knows the results with susceptible and with resistant strains in one place, one reasonably can predict the outcome of therapy anywhere.

Using Available Data to Predict Treatment Success

An optimized regimen is defined as one that reliably achieves 95% or greater cures in patients with susceptible organisms. Although the effectiveness of any regimen can be undermined by antimicrobial resistance, the effect of resistance is not random and the effect of any particular level of resistance can be estimated based on studies with that combination elsewhere, for example, use of the

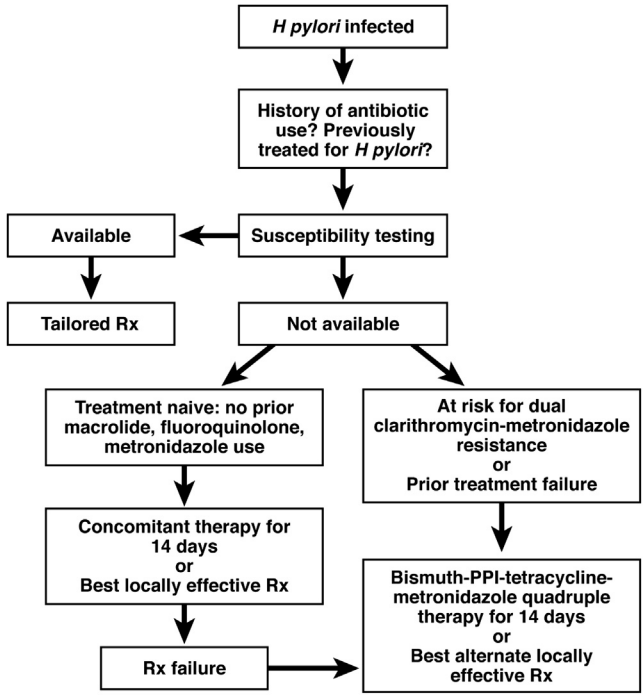


Figure 1. Recommended approach to treatment of *H pylori* infections. Rx, treatment.

optimized regimen (14-day concomitant therapy, consisting of a proton pump inhibitor [PPI], clarithromycin, metronidazole, and amoxicillin, given twice a day for 14 days).[10] The regimen contains 4 drugs, but for the purpose of understanding the effects of resistance can best be considered as the simultaneous administration of 2 triple therapies plus a dual therapy (eg, a PPI–amoxicillin-clarithromycin plus a PPI–amoxicillin-metronidazole plus a PPI-amoxicillin dual therapy). Both triple regimens individually will reliably achieve 95% or greater success PP with susceptible strains whereas the dual component will achieve approximately 50% success with clarithromycin- and metronidazole-resistant strains (ie, the strains are only susceptible to amoxicillin). If resistance to clarithromycin or metronidazole was not present, there would be no indication to use the 4-drug regimen. However, when resistance results in unacceptably low treatment success rates when either is used empirically, the 4-drug combination might be considered.

Unless there is an interaction between the antibiotics, the treatment population can be visualized as 4 separate subgroups: one group with organisms susceptible to all antibiotics, one group with only clarithromycin-resistant organisms, another group with only metronidazole-resistant organisms, and the final group with organisms resistant to both (here, we assume an absence of resistance to amoxicillin). The subgroups without resistance and those resistant to a single drug will each receive an optimized triple therapy for their infection and most will be cured, and the overall success thus will depend entirely on the success of the PPI-amoxicillin therapy for those with dual clarithromycin-metronidazole resistance.

In this example, both triple therapies achieve 97% treatment success and the dual therapy achieves 50% success (Table 1). One can calculate that treatment success will remain at or above 90% until dual resistance exceeds 15%. That calculation is based on the following formula: (% success with all-susceptible strains) (proportion with all-susceptible infections) + (% success with clari-susceptible strains) (proportion with clari-susceptible infections) + (% success with met-susceptible strains) (proportion with met-susceptible infections) + (% success with dual resistant strains) (proportion with dual resistant strains) = 90%. Because the success with organisms susceptible to all antibiotics and single-drug resistances is the same, the 2 triple therapies can be combined to simplify the calculation (eg, where X = the proportion with dual resistance, the formulas is 0.97 (1 − X) + 0.5 X = ~0.90, and thus X = 14.9%). Table 1 lists the approximate success rates with a number of common therapies.

Resistance Effects

Triple therapies containing a PPI and amoxicillin plus clarithromycin, metronidazole, a fluoroquinolone, or rifabutin all are extremely sensitive to resistance to the third drug. Resistance to clarithromycin, fluoroquinolones, and rifabutin cannot be overcome by increasing the dose or duration. By using the earlier-described formula one can calculate that 7-day clarithromycin-containing triple therapy will decrease to less than 90% success when clarithromycin resistance exceeds 5% (or 15% when the regimen is given for 14 days).

The 4-drug nonbismuth clarithromycin-containing sequential and concomitant therapies are extremely sensitive to dual clarithromycin-metronidazole resistance, which reduces the regimens to contain only the PPI-amoxicillin component. Because the prevalence of dual resistance has such a great effect, it is important to consider how dual resistance might be acquired and what clinical factors might help predict its prevalence. Probably the most important variable is whether dual resistance is acquired from one encounter with both drugs or from separate encounters. For example, the prevalence of metronidazole resistance in many developing countries is greater than 40%, and often is 80% or greater. In these countries both drugs are rarely given together and the prevalence of dual resistance depends primarily on the prevalence of clarithromycin resistance such that the proportion of patients with dual resistance will be approximately the same as the prevalence of clarithromycin resistance. In Nicaragua, the prevalence of metronidazole resistance is at least 80%, and thus dual resistance would exceed 15% whenever clarithromycin resistance exceeded 19% (ie, 80% of 19 = 15.2%).[11] In Southern Europe, metronidazole resistance is approximately 30% (Supplementary Figure 1),[12] and if acquisition of resistance to each drug were truly independent, clarithromycin resistance would need to exceed 50% to undermine 14-day concomitant therapy. However, even in low metronidazole resistance prevalence countries, pockets of high prevalence of metronidazole resistance often exist in which dual resistance may exceed 15% (eg, in women in whom metronidazole is used for trichomonas infections, immigrants from developing countries, and patients who previously failed sequential or PPI-clarithromycin-metronidazole triple therapy). For such high-risk groups, empiric concomitant or sequential therapies likely would be poor choices.

Table 1. Approximate Treatment Success PP With Susceptible Strains (Western Results)

Therapy	Days	Success rate
Clarithromycin triple therapy	7	94%
Clarithromycin triple therapy	14	97%
Sequential therapy	10	94%
Sequential therapy	14	97%
Hybrid therapy	14	97%
Fluoroquinolone triple therapy	7	<80%
Fluoroquinolone triple therapy	10	<90%
Fluoroquinolone triple therapy	14	96%
PPI + amoxicillin therapy[a]	5	10%
PPI + amoxicillin therapy[a]	7	15%
PPI + amoxicillin therapy	10	20%
PPI + amoxicillin therapy[a]	14	50%
PPI metronidazole triple therapy	7	94%
PPI metronidazole triple therapy	14	97%
PPI-bismuth tetracycline, metronidazole therapy	14	>95%

[a]Equals triple therapies but with clari-, met-, or fluoroquinolone-resistant infections.

Current Recommended Regimens

Caveat

It should be recognized that the data pool from which the outcomes of various therapies with susceptible and resistant organisms are available is not large, making the numbers we have used in our calculations imprecise, and our calculations are only approximations (Table 2). Sadly, the lack of data is related to the fact that resistance is not collected in most trials. Nonetheless, the results shown provide reasonable estimates of what can be expected, and the appendix to the recent article by Liou et al[13] provides additional details, comparisons, and sensitivity analyses, as well as a useful online calculator (https://hp-therapy.biomed.org.tw/) based on data from their comparison of 10- and 14-day sequential therapy and 14-day triple therapy in Taiwan.

The most variable results are probably those regarding the expected outcomes of PPI-amoxicillin dual therapies. However, this group generally represents only a small proportion of cases. The data used here primarily are derived from Western studies that have shown that

Table 2. *H pylori* Therapies Recommended for Empiric Therapy in Western Countries

For general use
14-day concomitant therapy
14-day bismuth quadruple therapy
14-day hybrid sequential-concomitant therapy
Areas where there is clarithromycin-metronidazole dual resistance <5%
14-day sequential therapy
With fluoroquinolone resistance
14-day fluoroquinolone triple therapy <13%
14-day fluoroquinolone bismuth therapy <25%
5-day fluoroquinolone concomitant therapy <20%
Salvage therapies (after ≤2 failures with different drug combinations)
Dependent on background rates of resistance and prior drug use by subject
One of the earlier-mentioned regimens
14-day furazolidone bismuth quadruple therapy
A rifabutin regimen, preferably for 14 days
Obsolete regimens for use only in special low-resistance populations
14-day clarithromycin-containing triple therapy
14-day metronidazole-containing triple therapy
10-day sequential therapy

NOTE. These are recommendations for populations. See text for details of therapies and for modifications when considering an individual patient.

14-day dual therapy yields approximately 50% success, and results greater than 50% are uncommon when using the doses and durations typically used with common therapies, and success decreases as the duration decreases. The actual results will depend in part on the effectiveness of the PPI in increasing the intragastric pH to high levels (eg, pH 6). PPI effectiveness depends in part on the PPI used, its dose and frequency of administration, the effects of CYP2C19 on the metabolism of the PPI[14] (and potentially some antibiotics), as well as the ability of the stomach to produce acid. The results reported here probably err slightly on the optimistic side but are consistent with the use of the formulas described previously with data from clinical trials.

Concomitant Therapy

Meta-analyses have shown that the outcome of concomitant therapy (PPI-amoxicillin 1 g, clarithromycin 500 mg, metronidazole/tinidazole 500 mg, all twice daily for 14 days) is duration dependent,[15,16] which was confirmed in a recent head-to-head comparison of 5- and 10-day concomitant therapies in Thailand, where 5-day therapy proved unsatisfactory,[17] and by failure of 5-day concomitant therapy in Central and South America (ie, regions with known high levels of metronidazole resistance).[18] The Achilles' heel of concomitant therapy is dual metronidazole-clarithromycin resistance. Fourteen-day concomitant therapy is a preferred initial empiric therapy for areas and patient groups in whom dual resistance is unlikely, but is not recommended as a first-line empiric regimen where metronidazole resistance is likely greater than 60%, such as China, Iran, India, central and South America, or in populations at high risk of dual resistance (ie, after clarithromycin or metronidazole treatment failures).

Hybrid Therapy

Hybrid therapy (PPI, amoxicillin 1 g for 14 days with amoxicillin 1 g, clarithromycin 500 mg, metronidazole/tinidazole 500 mg given for the final 7 days, all twice a day) combines sequential and concomitant therapy because all 4 drugs are given together. This is a new regimen with only a few published studies.[10,19,20] In a head-to-head comparison with 14-day concomitant therapy they appeared to be equivalent, albeit hybrid therapy was more complicated. Further studies are needed to identify if there are important differences in relation to success in the face of different patterns of resistance. It could be considered in the same populations in whom concomitant therapy is recommended; 14-day hybrid therapy is expected to decrease to less than 90% when clarithromycin-metronidazole resistance exceeds 9%.

Bismuth Quadruple Therapy

Bismuth quadruple therapy (PPI twice daily, bismuth 4 times daily, tetracycline HCl 500 mg 4 times daily, metronidazole 500 mg 3 times daily for 14 days) is the oldest effective therapy and still one for which we do not yet know the optimal dose. With attention to detail regarding the dose and duration, the primary Achilles' heel is compliance. Tetracycline resistance is rare but currently many countries are experiencing a general unavailability of tetracycline. Generally, doxycycline is not an adequate substitute.

By using this regimen at full doses and for 14 days one can expect 95% or greater treatment success irrespective of the level of metronidazole resistance.[21,22] Therapy for 7 and probably for 10 days is very susceptible to metronidazole resistance; however, the prevalence of resistance, which results in a decrease in outcome to less than 90%, is probably approximately 30%.[23]

This regimen also has the most unanswered questions regarding the optimal doses and frequency of drug administration. For example, in Italy, dosing only with the mid-day and evening meals was effective despite a dose reduction to half of the recommend dose.[24,25] Treatment with resistant strains was less effective when administered at breakfast and the evening meal.[26] Recent studies from China in a population with essentially universal metronidazole resistance also used twice-daily bismuth and full 4 times daily doses and dosing intervals for the antibiotics with excellent results.[22]

Because of the relative high rate of side effects, optimization is needed in terms of formulations, forms of bismuth, doses, and dosing intervals, as well as effectiveness in relation to the minimal inhibitory concentrations of metronidazole. Two caveats: the Etest

overestimates the prevalence of metronidazole resistance such that resistance always should be confirmed (eg, by agar dilution) for an accurate estimation of effectiveness in the presence of resistance.[27,28]

Therapies Generally Recommended Only for Geographic Areas With a Low Prevalence of Resistance

Clarithromycin-Containing Triple Therapy

Despite the Maastricht IV recommendations, clarithromycin-containing triple therapy (PPI, amoxicillin 1 g, clarithromycin 500 mg, all twice a day for 14 days) is an obsolete therapy whether given for 7, 10, or 14 days.[29] The Achilles' heel is clarithromycin resistance, with success depending on clarithromycin resistance and the duration of therapy (Tables 1 and 3). With 14-day therapy the combination remains effective until clarithromycin resistance exceeds approximately 15%, whereas 7-day therapy is compromised by clarithromycin resistance exceeding 5%. Currently, there are few regions in the world where clarithromycin resistance is less than 15% (ie, the 14-day regimen is still useful in such areas as Northern Europe and Thailand). Clarithromycin triple therapy has been superceded by 14-day concomitant therapy, whose only Achilles' heel is dual clarithromycin-metronidazole resistance.

Metronidazole-Containing Triple Therapy

The Achilles' heel of metronidazole-containing triple therapy (PPI, amoxicillin 1 g, metronidazole/tinidazole 500 mg, all twice a day for 14 days) is metronidazole resistance, and metronidazole-containing triple therapy now rarely is used except as a tailored therapy or in Japan where the general use of metronidazole has been strongly discouraged by the government because of possible genotoxicity.[30,31] Overall success parallels the experience with clarithromycin-containing triple therapy in relation to duration and the presence of resistance.

Table 3. Achilles' Heel of Individual Common Regimens

Optimized therapies	Achilles' heel[a]
14-day clarithromycin triple therapy	Clar® >15%
14-day metronidazole triple therapy	Met® >15%
14-day concomitant therapy	Clari®-Met® dual® >15%
14-day sequential therapy	Clari®-Met® dual® >5%
14-day hybrid therapy	Clari®-Met® dual® >9%
14-day fluoroquinolone triple therapy	Levo® >13%
14-day fluoroquinolone bismuth quadruple therapy	Levo® >25%[b]
14-day bismuth quadruple therapy	Tetracycline resistance (rare), compliance
14-day bismuth-furazolidone therapy	Furazolidone resistance (rare), compliance
5-day fluoroquinolone sequential therapy	Levo® ~20%[b]

Clar, clarithromycin; Levo, levofloxacin; Met, metronidazole.
[a]The resistance level (®) at which treatment success decreases to less than 90%.
[b]The number of subjects receiving these regimens is low, such that the estimate is only approximate.

Sequential Therapy

Although 14-day sequential therapy (PPI–amoxicillin 1 g for 5 or 7 days followed by a PPI–clarithromycin 500 mg–metronidazole/tinidazole 500 mg all twice daily, for 5 or 7 days) provides better results than 10-day therapy, both have the same Achilles' heel (ie, dual resistance and metronidazole resistance)[13] (Table 3). Metronidazole resistance undermines 10-day sequential therapy when it reaches 20% and 14-day sequential therapy at approximately 30% (Table 4). The regimens

Table 4. Effect of Metronidazole Resistance on 10- and 14-Day Sequential and 14-Day Triple Therapies

	10-day sequential			14-day sequential						14-day triple		
	Metronidazole resistance, >20%; clarithromycin resistance, 0			Metronidazole resistance, 20%; clarithromycin resistance, 18%			Metronidazole resistance, 30%; clarithromycin resistance, 6%			Metronidazole resistance, N/A; clarithromycin resistance, 15%		
Treatment scenario pattern[a]	Success[b]	%[c]	n[d]	Success	%	n	Success	%	n	Success	%	n
Cs-Ms	95%	80	76	99%	65.6	65	99%	65.8	65	97%	85	82.5
Cr-Ms	80%	0	0	88%	14.4	12.6	88%	4.2	3.7	50%	15	7.5
Cs-Mr	75%	20	15	75%	16.4	12.3	75%	28.2	21	N/A	-	—
Cr-Mr	10%	0	0	15%	3.6	0.5	15%	1.8	0.3	N/A	-	—
Overall success			91			90.4			90			90

N/A, not applicable.
[a]Resistance pattern in population ranging from clarithromycin susceptible (Cs) and metronidazole susceptible (Ms) to dual resistance (Cr-Mr).
[b]Predicted treatment success for the pattern of resistance.
[c]Percentage of the study population with that pattern of resistance.
[d]Success rate percentage of the resistant pattern group with successful therapy.

are complicated, and successful use is restricted to regions where clarithromycin resistance is high and metronidazole resistance is low.

Table 4 shows that at 20% metronidazole resistance, success with 10-day sequential therapy is approximately 90% PP and any level of clarithromycin resistance would cause it to decrease further. In contrast, despite 20% metronidazole resistance, success with 14-day sequential therapy remains greater than 90% until clarithromycin resistance exceeds 18%. There are instances when 14-day triple therapy will be superior to sequential therapy because it is not affected by metronidazole resistance and can withstand up to 15% clarithromycin resistance before decreasing to less than 90% success. The primary Achilles' heel for sequential therapy is metronidazole resistance (ie, the level of metronidazole resistance determines the level of clarithromycin resistance required for success to decrease to <90%). If metronidazole resistance is absent or low, sequential therapy for 10 or 14 days is very resistant to clarithromycin resistance (eg, ~30% for 10 days and ~80% for 14 days), but in that instance 14-day metronidazole triple therapy or concomitant therapy likely would be better choices. Because 10-day sequential therapy fails when metronidazole resistance exceeds 20% or clarithromycin-metronidazole dual resistance is greater than 5%, sequential therapy has had a poor showing in Asia and South and Central America[13,32] (eg, in Taiwan, 10-day sequential therapy achieved 78.9% success despite no clarithromycin resistance).[13]

Fluoroquinolone-Containing Triple Therapy

Only 14-day therapy is successful with fluoroquinolone triple therapy (PPI twice daily, amoxicillin 1 g twice daily, a fluoroquinolone once a day such as levofloxacin, moxifloxacin, or sitofloxacin, for 14 days). However, success is restricted to areas with low fluoroquinolone resistance. Fluoroquinolone resistance cannot be overcome by increasing the dose or duration of triple therapy, which becomes ineffective when resistance reaches 13%. Fluoroquinolone therapy is not recommended for patients who have received any fluoroquinolone in the past or in areas where fluoroquinolone resistance exceeds 10%. Possibly better fluoroquinolone-containing regimens include fluoroquinolone-bismuth therapy and fluoroquinolone concomitant therapy. Neither has been optimized or tested widely and generally they should be used as tailored therapies (see later).

Fluoroquinolone Bismuth Therapy

Fluoroquinolone bismuth therapy (PPI twice daily, amoxicillin 1 g twice daily, bismuth twice daily, levofloxacin 500 mg once daily for 14 days) is basically the addition of bismuth to fluoroquinolone triple therapy. The addition of bismuth is estimated to maintain effectiveness with fluoroquinolone resistance as high as 25%. This regimen also has not been optimized or tested except in China, but likely would be a better empiric choice than 14-day fluoroquinolone triple therapy in most regions.

Fluoroquinolone Concomitant Therapy

Fluoroquinolone concomitant therapy (PPI [esomeprazole 40 mg or equivalent], amoxicillin 1 g, levofloxacin 500 mg, tinidazole/metronidazole 500; all twice daily for 5 days) has been calculated to remain effective with fluoroquinolone resistance less than 20% to 25%, or metronidazole resistance less than 50%, but would be ineffective if dual resistance exceeded approximately 10%.[33] The regimen has been reported in only 1 study[34] and has not been optimized in terms of doses (likely 500 mg of levofloxacin would be sufficient) or duration.

Salvage Therapies: After at Least 2 Treatment Failures With Different Regimens

Furazolidone Bismuth Quadruple Therapy

There are a number of different formulations but most successful ones are based on bismuth quadruple therapy. One substitutes furazolidone (100 mg 3 times daily) for metronidazole in 14-day bismuth quadruple therapy. Another substitutes amoxicillin (1 g 3 times daily) for tetracycline. Both have proven highly effective in China[22] and may prove especially useful in areas where furazolidone is available and tetracycline is difficult to obtain.

Furazolidone is only available in a limited number of countries but it is a highly effective antimicrobial and resistance generally is low. Furazolidone is a monoamine oxidase inhibitor and interacts with numerous other drugs and foods such that an avoidance sheet always should be provided to the patient to reduce the rate of unnecessary side effects.[35] Where it is available it is an excellent salvage regimen but one where side effects are to be expected.

Rifabutin-Containing Regimens

Rifabutin is used primarily as an antituberculosis drug. Resistance among *H pylori* is rare. The initial trials, particularly as a 7-day triple therapy, proved disappointing,[36] but several regimens are promising and it is expected that an optimized rifabutin soon will be identified for use especially as a salvage therapy. The original successful trial (ie, 96.6%) consisted of rifabutin 150 mg daily, amoxicillin 1.5 g 3 times daily, and pantoprazole 80 mg (or an equivalent PPI) 3 times daily for 12 days.[37] We have used this regimen with success as a salvage therapy

when given for 14 days. More recent studies have tested lower doses of amoxicillin and PPI (rifabutin 150 mg once daily, amoxicillin 1 g twice daily, and esomeprazole 40 mg twice daily for 12 days) with results as low as 88.6%.[38] Clearly, additional studies are needed to optimize the regimen in terms of dose and duration. Finally, a recent study from Western Australia evaluated the combination of a PPI, bismuth, rifabutin, and ciprofloxacin, and reported an eradication rate of 95.2% in susceptible strains.[39] The recent increase in fluoroquinolone resistance makes it unlikely that the combination will prove useful as other than a tailored regimen, but it brings up the intriguing question regarding how much improvement, if any, would be obtained by the addition of bismuth to rifabutin triple therapy.[40]

Second or Subsequent Treatments for Treatment Failures

Generally, clinicians should have 2 preferred first-line regimens known to be effective locally, with the choice between them based on the patients history of prior drug use and exposure (Figure 2). The regimen with the highest predicted successful outcome always should be used first.[41] Treatment success always should be confirmed, generally using a noninvasive test for active infection such as the stool antigen or urea breath test.[42] Confirmation of cure also provides the clinician with an early warning of the development of increasing resistance in the community.

H pylori is naturally resistant to many antimicrobials and rapidly has become resistant to others. The use of agents to which the organism is resistant either naturally or by acquired resistance has no effect on the outcome of therapy with agents to which the strain is susceptible. Prior use of an antibiotic for another infection often results in the *H pylori* becoming resistant (a bystander effect), and clarithromycin and other macrolides, fluoroquinolones, and rifabutin should not be used again. Generally, amoxicillin and tetracycline can be re-used because resistance rarely develops. The key outcome variable is whether the infecting strain is susceptible. In our experience, the same high success rates are obtained with the first and the nth-line regimen, provided the organisms are susceptible and good compliance is obtained. To the infection, all attempts with agents to which it is susceptible are first attempts. We do not know whether some patients may be more difficult to cure than others but, all things being equal, the effectiveness of first-line agents, first-line alternative agents, or even salvage therapies is similar if the organisms are susceptible. Repeated failures should prompt assessment of compliance and rare events such as the development of amoxicillin resistance.

Compliance and Adherence

Poor compliance with a regimen and antimicrobial resistance are the primary reasons for failure of what is otherwise a reliably excellent regimen. Large multicenter clinical trials have shown that although side effects related to the antibiotics used are common, in the majority of trials the drop-out rates because of side effects are low (eg, in the range of 5%). Although there is considerable literature regarding compliance with medication use, treatment of *H pylori* has not been a popular area of such research. The fact that *H pylori* therapy often involves multiple drugs and multiple dosing intervals makes patient education extremely important. Emphasizing the importance of taking all the drugs, as generally performed in large multicenter studies, repeatedly has shown that this is associated with a high degree of compliance despite the complexity of some regimens. When tested in a randomized trial, patient counseling and follow-up evaluation have been shown to improve the outcome and compliance of *H pylori* therapy and is recommended.[43] It is worthwhile to consider direct counseling regarding the regimen and the need to be compliant as well as to give handouts regarding the objectives and the details of the regimen. Although it is important to try to keep patients on therapy despite side effects, it also is important to test

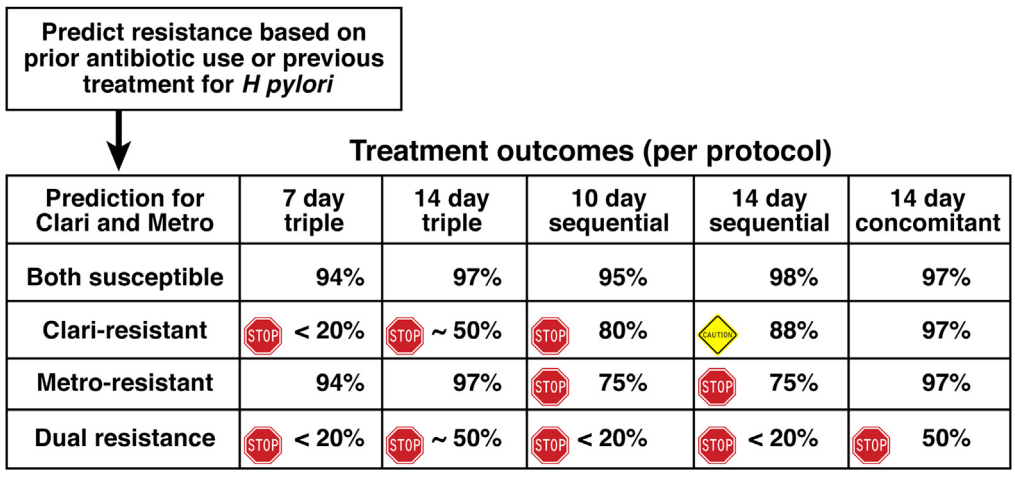


Figure 2. Example of choices of clarithromycin-containing regimens for an individual patient based on predicted resistance to clarithomycin and metronidazole.

for cure even if patients were unable to complete the regimen because even a short course of therapy will cure a proportion of patients.

Recommendations Regarding Developing New Regimens

The trial-and-error approach to the development of *H pylori* therapies has proven to be inefficient and to provide misleading results. The history of sequential therapy is a good example. Originally, 10-day sequential therapy was devised in response to failure of triple therapy in Italy[44,45] and it proved to be successful and superior to triple therapy.[46] Unfortunately, it was presumed to be optimal and no further attempts were made to optimize it or to systematically examine its limitations. Rather, sequential therapy was repeated in the same population to prove its superiority to triple therapy. These multiple samplings then were combined in meta-analyses to confirm that, at least in that population, sequential therapy was superior to triple therapy.[47–49] Importantly, the detrimental effect of clarithromycin resistance was noted, but the critical effect of metronidazole resistance on outcome remained unrecognized.[32] When sequential therapy was tested in Southern Italy and other populations with higher metronidazole resistance, it generally failed to achieve its prior success.[32,50,51] The process took approximately 10 years, during which thousands of subjects were randomized to triple therapy, which repeatedly had been proven to provide unacceptable results[1,52]; many meta-analyses were performed but the severe limitations of the regimen remained unrecognized. It finally was optimized in 2013.[13] Additional details are available in the Supplementary Material.

Summary Recommendations

Sufficient data from treatment trials in which the outcomes in relation to susceptibility resistance have been provided to allow an evidence-based approach to choosing anti–*H pylori* therapies. We now can add to the admonition to use what works locally by being able to reliably identify which regimens have the greatest chance of working. Figure 1 outlines a general schema, with therapy chosen based on pretreatment susceptibility testing, or, if unavailable, based on a combination of local experience and information obtained from the patients and the patients' records. The earlier-described data and discussions generally focused on therapeutic choices for a population. Whether one considers an individual patient (ie, population = n of 1) or a group, the outcome variables are determined by resistance and compliance. Figure 2 shows how suspected resistance markedly influences the choice for an individual subject (eg, previous use of a macrolide or metronidazole would make triple or sequential therapy poor choices) such that what might be recommended for a population often differs when individualized to a single patient.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2013.05.028.

References

1. Graham DY. *Helicobacter pylori* eradication therapy research: ethical issues and description of results. Clin Gastroenterol Hepatol 2010;8:1032–1036.
2. Graham DY, Fischbach LA. Empiric therapies for *Helicobacter pylori* infections. CMAJ 2011;183:E506–E508.
3. Rimbara E, Fischbach LA, Graham DY. Optimal therapy for *Helicobacter pylori* infections. Nat Rev Gastroenterol Hepatol 2011;8:79–88.
4. Sheiner LB, Rubin DB. Intention-to-treat analysis and the goals of clinical trials. Clin Pharmacol Ther 1995;57:6–15.
5. Broutet N, Marais A, Lamouliatte H, et al. cagA Status and eradication treatment outcome of anti-*Helicobacter pylori* triple therapies in patients with nonulcer dyspepsia. J Clin Microbiol 2001;39:1319–1322.
6. Scaccianoce G, Hassan C, Panarese A, et al. *Helicobacter pylori* eradication with either 7-day or 10-day triple therapies, and with a 10-day sequential regimen. Can J Gastroenterol 2006; 20:113–117.
7. Suzuki T, Matsuo K, Ito H, et al. Smoking increases the treatment failure for *Helicobacter pylori* eradication. Am J Med 2006; 119:217–224.
8. Taneike I, Nami A, O'Connor A, et al. Analysis of drug resistance and virulence-factor genotype of Irish *Helicobacter pylori* strains: is there any relationship between resistance to metronidazole and cagA status? Aliment Pharmacol Ther 2009; 30:784–790.
9. Zullo A, Perna F, Hassan C, et al. Primary antibiotic resistance in *Helicobacter pylori* strains isolated in northern and central Italy. Aliment Pharmacol Ther 2007;25:1429–1434.
10. Molina-Infante J, Romano M, Fernandez-Bermejo M, et al. Optimized non-bismuth quadruple therapies cure most patients with *Helicobacter pylori* infection in populations with high rates of antibiotic resistance. Gastroenterology 2013;145:121–128.
11. Graham DY, Gonzalez C, Palacios C, et al. Importance of determining the pattern of *H. pylori* resistance in countries with a high prevalence of gastric cancer such as Nicaragua. Helicobacter 2011;11(Suppl 1):136.
12. Megraud F, Coenen S, Versporten A, et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut 2013;62:34–42.
13. Liou JM, Chen CC, Chen MJ, et al. Sequential versus triple therapy for the first-line treatment of *Helicobacter pylori*: a multicentre, open-label, randomised trial. Lancet 2013; 381:205–213.
14. Furuta T, Graham DY. Pharmacologic aspects of eradication therapy for *Helicobacter pylori* infection. Gastroenterol Clin North Am 2010;39:465–480.
15. Essa AS, Kramer JR, Graham DY, et al. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant

therapy" versus triple therapy for *Helicobacter pylori* eradication. Helicobacter 2009;14:109–118.
16. Gisbert JP, Calvet X. Review article: non-bismuth quadruple (concomitant) therapy for eradication of *Helicobacter pylori*. Aliment Pharmacol Ther 2011;34:604–617.
17. Kongchayanun C, Vilaichone RK, Pornthisarn B, et al. Pilot studies to identify the optimum duration of concomitant *Helicobacter pylori* eradication therapy in Thailand. Helicobacter 2012;17:282–285.
18. Greenberg ER, Anderson GL, Morgan DR, et al. 14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial. Lancet 2011;378:507–514.
19. Sardarian H, Fakheri H, Hosseini V, et al. Comparison of hybrid and sequential therapies for *Helicobacter pylori* eradication in Iran: a prospective randomized trial. Helicobacter 2013; 18:129–134.
20. Hsu PI, Wu DC, Wu JY, et al. Modified sequential *Helicobacter pylori* therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (Hybrid) therapy for the final 7 days. Helicobacter 2011; 16:139–145.
21. Salazar CO, Cardenas VM, Reddy RK, et al. Greater than 95% success with 14-day bismuth quadruple anti-*Helicobacter pylori* therapy: a pilot study in US Hispanics. Helicobacter 2012; 17:382–389.
22. Liang X, Xu X, Zheng Q, et al. Efficacy of bismuth-containing quadruple therapies for clarithromycin-, metronidazole-, and fluoroquinolone-resistant *Helicobacter pylori* infections in a prospective study. Clin Gastroenterol Hepatol 2013; 11:802–807.
23. Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. Aliment Pharmacol Ther 2007; 26:343–357.
24. Dore MP, Farina V, Cuccu M, et al. Twice-a-day bismuth-containing quadruple therapy for *Helicobacter pylori* eradication: a randomized trial of 10 and 14 days. Helicobacter 2011; 16:295–300.
25. Dore MP, Maragkoudakis E, Pironti A, et al. Twice-a-day quadruple therapy for eradication of *Helicobacter pylori* in the elderly. Helicobacter 2006;11:52–55.
26. Graham DY, Belson G, Abudayyeh S, et al. Twice daily (mid-day and evening) quadruple therapy for *H. pylori* infection in the United States. Dig Liver Dis 2004;36:384–387.
27. Osato MS, Reddy R, Reddy SG, et al. Comparison of the Etest and the NCCLS-approved agar dilution method to detect metronidazole and clarithromycin resistant *Helicobacter pylori*. Int J Antimicrob Agents 2001;17:39–44.
28. Osato MS, Graham DY. Etest for metronidazole susceptibility in *H. pylori*: use of the wrong standard may have led to the wrong conclusion. Am J Gastroenterol 2004;99:769.
29. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of *Helicobacter pylori* infection–the Maastricht IV/ Florence Consensus Report. Gut 2012;61:646–664.
30. Hori K, Miwa H, Matsumoto T. Efficacy of 2-week, second-line *Helicobacter pylori* eradication therapy using rabeprazole, amoxicillin, and metronidazole for the Japanese population. Helicobacter 2011;16:234–240.
31. Graham DY, Rimbara E. *Helicobacter pylori* therapy in the west. Japanese J Helicobacter Res 2012;13:4–9.
32. Gisbert JP, Calvet X, O'connor A, et al. Sequential therapy for *Helicobacter pylori* eradication: a critical review. J Clin Gastroenterol 2010;44:313–325.
33. Graham DY, Shiotani A. Which therapy for *Helicobacter pylori* infection? Gastroenterology 2012;143:10–12.
34. Federico A, Nardone G, Gravina AG, et al. Efficacy of 5-day levofloxacin-containing concomitant therapy in eradication of *Helicobacter pylori* infection. Gastroenterology 2012;143:55–61.
35. Graham DY, Lu H. Furazolidone in *Helicobacter pylori* therapy: misunderstood and often unfairly maligned drug told in a story of French bread. Saudi J Gastroenterol 2012;18:1–2.
36. Gisbert JP, Calvet X. Review article: rifabutin in the treatment of refractory *Helicobacter pylori* infection. Aliment Pharmacol Ther 2012;35:209–221.
37. Borody TJ, Pang G, Wettstein AR, et al. Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant *Helicobacter pylori* infection. Aliment Pharmacol Ther 2006;23:481–488.
38. Fiorini G, Vakil N, Zullo A, et al. Culture-based selection therapy for patients who did not respond to previous treatment for *Helicobacter pylori* infection. Clin Gastroenterol Hepatol 2013;11:507–511.
39. Tay CY, Windsor HM, Thirriot F, et al. *Helicobacter pylori* eradication in Western Australia using novel quadruple therapy combinations. Aliment Pharmacol Ther 2012;36:1076–1083.
40. Graham DY, Gisbert JP. *Helicobacter pylori*: tailored therapy with novel sequential quadruple therapies. Nat Rev Gastroenterol Hepatol 2013;10:6–8.
41. Graham DY, Calvet X. Guide regarding choice of second-line therapy to obtain a high cumulative cure rate. Helicobacter 2012;17:243–245.
42. Attumi TA, Graham DY. Follow-up testing after treatment of *Helicobacter pylori* infections: cautions, caveats, and recommendations. Clin Gastroenterol Hepatol 2011;9:373–375.
43. Al-Eidan FA, McElnay JC, Scott MG, et al. Management of *Helicobacter pylori* eradication–the influence of structured counselling and follow-up. Br J Clin Pharmacol 2002;53:163–171.
44. Buzas GM. Gastric tubes as vectors of *Helicobacter pylori* transmission. Med Hypotheses 2010;75:47–49.
45. Laheij RJ, Rossum LG, Jansen JB, et al. Evaluation of treatment regimens to cure *Helicobacter pylori* infection–a meta-analysis. Aliment Pharmacol Ther 1999;13:857–864.
46. Zullo A, Rinaldi V, Winn S, et al. A new highly effective short-term therapy schedule for *Helicobacter pylori* eradication. Aliment Pharmacol Ther 2000;14:715–718.
47. Jafri NS, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment. Ann Intern Med 2008;148:923–931.
48. Gatta L, Vakil N, Leandro G, et al. Sequential therapy or triple therapy for *Helicobacter pylori* infection: systematic review and meta-analysis of randomized controlled trials in adults and children. Am J Gastroenterol 2009;104:3069–3079.
49. Zullo A, De FV, Hassan C, et al. The sequential therapy regimen for *Helicobacter pylori* eradication: a pooled-data analysis. Gut 2007;56:1353–1357.
50. Iovene MR, Romano M, Pilloni AP, et al. Prevalence of antimicrobial resistance in eighty clinical isolates of *Helicobacter pylori*. Chemotherapy 1999;45:8–14.
51. Romano M, Cuomo A, Gravina AG, et al. Empirical levofloxacin-containing versus clarithromycin-containing sequential therapy for *Helicobacter pylori* eradication: a randomised trial. Gut 2010; 59:1465–1470.

52. Pounder RE, Talley NJ. Letter: the ethics of using inferior regimens in *H. pylori* randomised trials–editors' reply. Aliment Pharmacol Ther 2012;35:858.

Reprint requests
Address requests for reprints to: David Y. Graham, MD, Michael E. DeBakey Veterans Affairs Medical Center, RM 3A-318B (111D), 2002 Holcombe Boulevard, Houston, Texas 77030. e-mail: dgraham@bcm.edu; fax: (713) 790-1040.

Conflicts of interest
This author discloses the following: David Graham is an unpaid consultant for Novartis in relation to vaccine development for the treatment or prevention of *Helicobacter pylori* infection, a paid consultant for RedHill Biopharma regarding novel *H pylori* therapies and for Otsuka Pharmaceuticals regarding diagnostic testing; and has received royalties from Baylor College of Medicine patents covering materials related to the ^{13}C-urea breath test. The remaining authors disclose no conflicts.

Funding
Supported in part by the Office of Research and Development of the Medical Research Service Department of Veterans Affairs, a Public Health Service grant (DK56338) that funds the Texas Medical Center Digestive Diseases Center (DK067366 and CA116845 to D.Y.G.). The contents are solely the responsibility of the authors and do not necessarily represent the official views of the Department of Veterans Affairs or the National Institutes of Health. Also supported by research grants from the National Science Council of Taiwan for research into the prevention of gastric cancer and the pathogenesis of *Helicobacter pylori* (Y.-C.L. and M.-S.W.), and by grants from the National Center of Excellence for Clinical Trial and Research in the National Taiwan University Hospital for the foundation of the Taiwan Helicobacter Consortium (M.-S.W.).

Supplementary Material

Recommendations for New Regimens

The goal of the first experiment is to provide definitive data (ie, allow a "go" or "no go" decision). One should never need to ask whether the results would have been better if we had increased the duration, dose, dosing interval, and so forth. To prevent this, the initial study must use full doses and the maximum reasonable duration. Thus, the initial study should use full doses and the duration should be 14 days (ie, 14 days generally is considered the upper limit for duration and there are numerous examples in which 7- or 10-day regimens proved inferior to 14-day therapy). For example, hundreds of patients received fluoroquinolone, PPI, amoxicillin triple therapy before it was recognized that 95% cure rates could be achieved with 14-day therapy.[1]

The initial experiments should be a pilot study with predefined success (eg, at least 90% or 95% success PP) and include stopping rules to limit the exposure of subjects to unnecessary risks. The effect of resistance on outcome must be able to be assessed. This can be performed as a tailored regimen and only those with known pretreatment susceptible strains receive therapy, or biospy samples can be obtained and stored for after-the-fact assessment. Once good to excellent regimens are identified it is critical to know the effects of resistance, which can be tested directly in patients with known resistant strains, or this information can be obtained as part of empiric use trials. The lack of susceptibility data largely have been responsible for much of the confusion about the usefulness of both new and old therapies, and units that are unable to assess susceptibility should be precluded from performing exploratory clinical trials.

Optimizing Regimens

Optimization can include cost effectiveness, convenience, minimization of side effects, higher success in the presence of resistance to one or more components, and so forth. Only successful regimens should undergo optimization and optimization must not compromise outcome (eg, the original excellent success rate is maintained despite simplifying the regimen in terms of dosing, dosing interval, or duration). As noted earlier, optimization includes a study of the effects of changes in study parameters (eg, duration) on the results with resistant infections. For example, 7-day PPI bismuth quadruple therapy provides excellent results in the absence of metronidazole resistance but produces unacceptable low outcomes in the presence of metronidazole resistance. Thus, in some countries, 7-day therapy may be optimal whereas in other countries 14-day therapy is the minimum for an optimal result.

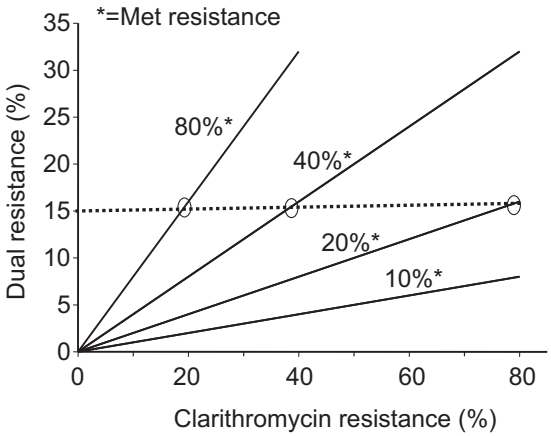
Avoiding Common Errors

Hopefully, the days in which trial and error is the primary approach used to identify new anti–*H pylori* regimens are nearing their end and will be replaced by approaches that are both efficient and logical.[2] Much of the current confusion related to how to best treat *H pylori* has resulted from poorly designed studies and attempts to understand failures while ignoring the critical role of resistance. For example, a recent large multicenter study of *H pylori* therapy in a South and Central America treatment trial did not take advantage of published data showing that metronidazole resistance was extremely high in the region and that prior studies with clarithromycin triple therapy typically had produced unacceptably low cure rates. The outcome of the trial was predictable (ie, Western regimens using clarithromycin and metronidazole would produce unacceptably low treatment success with the rank order favoring non–metronidazole-containing regimens).[3,4] Comparative trials also have remained a problem because the comparisons chosen generally have not been of good or excellent regimens, but primarily have been comparisons of ineffective regimes or good therapies with known ineffective regimens, the latter of which are, by definition, unethical.[5,6] As a result, meta-analyses generally have not provided useful information regarding which treatments to use and where. Another flaw of meta-analysis has been that comparisons of treatments that contain the same drugshave differed markedly in terms of details such as doses, durations, and adjuvants, and in relation to the populations examined, which often differed greatly in terms of the prevalence of resistance.[7,8] The results of meta-analysis have declared unacceptably low outcome regimens as equivalent or even as one superior to another despite the fact that both regimens produced unacceptably low outcomes.[7,9,10] Meta-analyses of suboptimal regimens, those that failed to account for resistance patterns, or compared entirely different doses and durations probably should neither be performed nor published. We can and should do better.

References

1. Miehlke S, Krasz S, Schneider-Brachert W, et al. Randomized trial on 14 versus 7 days of esomeprazole, moxifloxacin, and amoxicillin for second-line or rescue treatment of *Helicobacter pylori* infection. Helicobacter 2011;16:420–426.
2. Graham DY. Efficient identification and evaluation of effective *Helicobacter pylori* therapies. Clin Gastroenterol Hepatol 2009; 7:145–148.
3. Greenberg ER, Anderson GL, Morgan DR, et al. 14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial. Lancet 2011;378:507–514.

4. Graham DY, Trespalacios AA. Treatment of *Helicobacter pylori* in Latin America. Lancet 2012;379:408–409.
5. Graham DY. *Helicobacter pylori* eradication therapy research: ethical issues and description of results. Clin Gastroenterol Hepatol 2010;8:1032–1036.
6. Graham DY, Rimbara E. Understanding and appreciating sequential therapy for *Helicobacter pylori* eradication. J Clin Gastroenterol 2011;45:309–313.
7. Luther J, Higgins PD, Schoenfeld PS, et al. Empiric quadruple vs. triple therapy for primary treatment of *Helicobacter pylori* infection: systematic review and meta-analysis of efficacy and tolerability. Am J Gastroenterol 2010;105:65–73.
8. Gatta L, Vakil N, Leandro G, et al. Sequential therapy or triple therapy for *Helicobacter pylori* infection: systematic review and meta-analysis of randomized controlled trials in adults and children. Am J Gastroenterol 2009;104:3069–3079.
9. Li Y, Huang X, Yao L. e al. Advantages of moxifloxacin and levofloxacin-based triple therapy for second-line treatments of persistent *Helicobacter pylori* infection: a meta analysis. Wien Klin Wochenschr 2010;122:413–422.
10. Fuccio L, Minardi ME, Zagari RM, et al. Meta-analysis: duration of first-line proton-pump inhibitor based triple therapy for *Helicobacter pylori* eradication. Ann Intern Med 2007; 147:553–562.



Supplementary Figure 1. The effect of increasing metronidazole and clarithromycin resistance and the prevalence of dual clarithromycin-metronidazole resistance. When dual resistance equals 15% (*dotted line*), then 14-day concomitant therapy will cure less than 90% of patients. The proportion of patients with dual resistance is shown at different prevalences of metronidazole resistance, with the proportion with dual resistance plotted against the prevalence of clarithromycin resistance. As long as metronidazole resistance levels are less than 40%, the regimen is very resistant to typical increases in clarithromycin resistance. However, at high levels of resistance of either, only modest levels of resistance of the other will result in dual resistance exceeding the threshold level for treatment failure.