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Sequential therapy: Understanding and appreciating sequential therapy for *H. pylori* eradication

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Abstract

Despite the fact that sequential therapy has been evaluated in more than 2,500 patients and has been shown to on average provide *H. pylori* eradication in 90 to 94%, some authorities still question whether it should be a first-line anti-*H. pylori* regimen. Here, we discuss *H. pylori* eradication using experience and expectations with other common bacterial infections as a frame of reference. *H. pylori* is no exception and near 100% success is expected for optimized regimens treating susceptible infections. As such, the proper comparator would be the relation to 100% eradication. Superiority to another, often proven inferior, therapy per se provides little or no useful information. Treatment failures in infectious diseases are typically easily explainable and most often relate to the presence of antimicrobial resistance or failure to take the drugs. We provide a model for predicting the results of *H. pylori* combination therapies in relation to the pattern and prevalence of resistance. The results are consistent with clinical practice and explain why sequential is typically superior and essentially never inferior to triple therapy. We also show when meta-analysis is an inappropriate technique for the analysis of *H. pylori* clinical trials and discuss how to appropriately use of the technique. Finally, we discuss why the location of studies (e.g., Italy), is unimportant and explain why, from the standpoint of a therapy for an infectious disease, sequential therapy is a significant advance and should be considered one of the replacements for the outdated legacy triple therapy (proton pump inhibitor – clarithromycin – amoxicillin).

Keywords

proton pump inhibitors; *Helicobacter pylori*; amoxicillin; sequential therapy; triple therapy; meta-analysis; *H. pylori* eradication

Background

"Sequential therapy is not ready for prime time, but it is a promising approach that merits further study" [1]. "This is a promising therapy, but further trials are needed in other European countries and North America before it can be recommended as a first-line treatment" [2]. Are those recent conclusions correct? Sequential therapy [amoxicillin 1 g plus a proton pump inhibitor (PPI) b.i.d. for 5 days, then clarithromycin 500 mg and tinidazole or metronidazole 500 mg b.i.d plus a PPI b.i.d. for 5 days to complete 10 days of total therapy] was developed in response to the fact that in the majority of Europe and in the United States, a previous gold standard of legacy triple therapy (a PPI + amoxicillin + clarithromycin), when used as an empiric therapy, generally provided unacceptably low treatment success (i.e., 80% or less) [3] (i.e., the gold standard has transmuted into brass). In contrast, sequential therapy

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appeared to be a good substitute [4, 5]. For example, a review of 13 trials of sequential therapy showed that sequential therapy success was generally above 90% [2]. Based on the current patterns of resistance, treatment success with sequential therapy is not expected to fall below 90% in either the US or Europe. The results of more than 2,500 patients using sequential therapy have been reported and the effects of all possible variables have been discussed [2, 6]. What more might be needed?

Possibly those suggesting that more studies were needed were looking at the data the prospective of therapy for traditional gastrointestinal diseases rather than as treatment of an infectious disease. *H. pylori* differs markedly from other common gastrointestinal conditions in that one can reasonably expect to be able to eradicate the infection. There is also no placebo effect to consider as treatment success with placebo is essentially zero. With typical gastrointestinal diseases (e.g., IBD, GERD or constipation) the results of therapy of are scored as continuous variables and the results are often modest such as a 20% or 30% improvement in symptoms or healing, Proof of improvement always requires a comparator to ensure that the results are greater than would obtain with a placebo. The reason for the variability in response in most common gastrointestinal diseases is generally neither understood nor easily discoverable. In contrast, with common bacterial infectious diseases the success of therapy is judged in terms of prespecified endpoints, typically in relation to a 100% cure rate [7]. Treatment failures are rarely unexplainable and most often relate to the presence of antimicrobial resistance or failure to take the drugs [7].

Triple therapy, sequential therapy, bismuth quadruple therapy and a several other regimens all provide good to excellent results in the presence of *H. pylori* infections susceptible to those drugs (provided that one pays attention to the doses, durations of therapy and other important elements of therapy) [3] (Table 1). Here we will provide evidence why, from the standpoint of a therapy for an infectious disease, sequential therapy is a significant advance and should be considered one of the replacements for the outdated legacy triple therapy.

H. pylori as an infectious disease

Antimicrobial therapy of infectious diseases generally starts with identification and optimization of a regimen in terms of drug, dose, formulation, duration, etc [7]. Optimum is defined in terms of the ability to reliably cure in at least 95% of those with susceptible organisms. If resistance is rare, the regimen can be used empirically (i.e., without pretreatment antimicrobial susceptibility testing) until its success is undermined by the development of resistance. Declining effectiveness requires physicians to switch from an empiric strategy to one determined based on the results of susceptibility testing (i.e., therapy tailored to the results of susceptibility testing or simply tailored therapy). Among common infectious diseases, *H. pylori* infectious are somewhat unusual because successful therapy requires combinations of antimicrobials and often an antisecretory agent and also because susceptibility testing is generally not available, requiring physicians to rely on an empiric treatment strategy. Finally, few of the currently available regimens have been formally optimized as they were developed *ad hoc* without attempts to further optimize or improve their results [8]. However, clinical data are available for most antibiotic combinations that allow clinicians to predict the effects of resistance to one or more of the antibiotics and these data can be used to understand and compare regimens. Theoretically, if one knows the clinical outcome with susceptible strains and the effect of resistance to each antibiotic individually and as combinations, one should be able to predict the outcome for an individual patient, for a clinical trial if the pattern of resistance is known.

Model of results of therapy of sequential and other clarithromycin-containing therapies

Results of different *H. pylori* eradication trials of identical regimens (dose, duration, frequency of administration, etc) differ primarily because of differences in the patterns of resistance. If one prescribes sequential therapy to a patient with a clarithromycin resistant infection, clarithromycin drops out of the equation and the bacteria functionally receive therapy with a PPI + amoxicillin followed by a PPI + metronidazole. Empirically obtained knowledge of the outcome of such a regimen would allow the clinician to predict the effect on the outcome of trials in regions where the prevalence of clarithromycin differed. Table 2 illustrates the per protocol outcome of different clarithromycin-containing combinations in relation to the different patterns of resistance. First some caveats: the treatment success rates given are approximate and the reader can adjust them to test any "what if" hypotheses. The per protocol approach eliminates accounting for those who either do not complete the trial or do not take the medications and thus provides a better estimate of how well the regimen works [7]. However, it is important to note that same combination are present in many different regimens and the results for any one combination are expected to be the same and independent of the regimen or the region where the experiment was done. One can also use the results of clinical trials to work backwards and generally estimate what the pattern of resistance must be in the region where the study was performed.

Figure 1 shows an example of a trials of four clarithromycin-containing regimens in a population whose susceptibility pattern is 20% clarithromycin resistant, 20% metronidazole resistant and 0% amoxicillin resistant (i.e., of 100 subjects 64 would be susceptible to all agents, 16 each would be clarithromycin resistant and metronidazole susceptible, 16 would be metronidazole resistant and clarithromycin susceptible and 4 would be resistant to both clarithromycin and metronidazole (dual resistance).

Clearly, two factors drive the differences in outcome (i.e., the prevalence of clarithromycin resistance and of dual clarithromycin and metronidazole resistance). The presence of dual resistance theoretically removes both clarithromycin and metronidazole leaving only the PPI + amoxicillin dual regimen. Fourteen day dual therapy with standard dose PPI provides approximately 50% treatment success and approximately one-half that at 7 days [9, 10]. These results are subject to the prevelance of CYP2C19 polymorphisms and PPI dose as those slow PPI metabolizers or those receiving higher PPI doses will produce better results [11, 12].

The proportion with dual clarithromycin metronidazole resistance depends in part on the events surrounding development of resistance. For example, if they were independent (e.g., metronidazole for diarrhea and at a different time a macrolide for an upper respiratory infection (as modeled in the example) the prevalence of dual resistance will be lower than the prevalence of clarithromycin resistance (e.g,, for 30% clarithromycin resistance and 60% metronidazole resistance the proportion with dual resistance would be 18%). In contrast, if dual resistance was the result of simultaneous use of both agents, such as with a Bazzoli-type triple therapy [13], the frequency of dual resistance would be expected to be approximately equal to the prevalence of clarithromycin resistance with a corresponding reduction in overall treatment success. As such sequential therapy would be a less favorable choice for a salvage therapy [14].

Typically the factor with the largest effect on outcome is the proportion with clarithromycin resistance. With triple therapy, loss of clarithromycin leaves only the PPI + amoxicillin. In contrast, with sequential therapy, the residual is PPI + metronidazole dual therapy. The relatively high success with sequential therapy in the presence of clarithromycin resistance was unexpected and is the key to the success of sequential therapy. The lack of a large

number of trials with susceptibility data does not allow one predict the true average response and it may also depend other factors as discussed below. This lack of data despite more than 2,500 patients being studied is discouraging especially since simply putting away a biopsy frozen in transport media or the sample used for rapid urease testing would allow batch susceptibility testing and would have potentially prevented the many patients who received legacy triple therapy in comparative trials [7, 8, 15].

One would expect that treatment success with only a PPI + metronidazole dual therapy to be less than 25%, probably less than 10% success (ignoring the independent effect of the initial dual PPI + amoxicillin component). This unexpected results must be related to the effects of the initial PPI + amoxicillin dual therapy. However, there is no reason to postulate a residual effect of amoxicillin on the remaining population of bacteria as that population is predicted by the prevalence of pretreatment clarithromycin resistance. *H. pylori* with mutations in the ribosomal clarithromycin binding sites which do not allow binding of the drug and disruption of protein synthesis are resistant and postulated events such as one preventing achieving sufficient intracellular concentrations of the antibiotic are irrelevant. We believe that the effect is directly related to the marked reduction in bacterial load associated with the pretreatment with amoxicillin and the PPI (reduction or elimination of the inoculum effect) [16]. Possible effects of this reduction are a change in susceptibility of the residual organisms, an increased effectiveness of PPI metronidazole dual therapy, or both.

The location(s) of the small number of residual bacteria is unknown but probably most are in a semi-dormant state (a persister population) which explains the inability of amoxicillin to eradicate them [3, 17]. It is possible that pretreatment susceptibility testing of a small sample of the original proportion provided misleading information in terms of the residual population. Most infections are actually mixed [18–24] and the determination of “resistant” is due to outgrown of the resistant subpopulation. It is possible that clarithromycin resistant organism have a selective disadvantage in the presence of the stress of the PPI + amoxicillin dual therapy such that the residual population is biased toward survival of susceptible or less resistant strains (i.e. particular mutations which differ in the degree of resistance may be favored) [25]. This hypothesis could be tested by in situ hybridization (FISH) of biopsies taken at the end of the initial dual component of therapy.

The alternate, but not mutually exclusive, hypothesis is that the PPI + metronidazole regimen is more effective in very low density infections such as is present at this time allowing metronidazole alone to eradicate most of the residual infections.

Meta-analyses failed to provide clinically useful answers to the sequential therapy question

One goal of antibiotic treatment trials of *H. pylori* infections is to identify good therapies (i.e., those that reliable cure >90 or >95% of infections) [15, 26]. A good therapy does not somehow become better if a meta-analysis shows it to be superior to a bad therapy and we do not believe that anything useful is to be gained by formally comparing good and bad regimens. More importantly, trials that knowingly include an inferior therapy are likely to have been unethical and if so should neither be published nor be the subject of a meta-analysis [7].

Meta-analyst’s often remind me of the early Judy Garland and Mickey Rooney movies in which the response to any problem was “Let’s put on a show”. Modern investigators do not perform shows, rather they perform meta-analyses. Meta-analysis are unquestionably an advance in that they combine the results of studies that address a set of related research hypotheses and provides a common measure of effect size. As noted above, *H. pylori*

infection differs markedly from other common gastrointestinal conditions in that cure can reasonably be expected, there is also no placebo effect, and success of a therapy is best judged in terms of prespecified criteria such as ≥95% eradication. As noted below, meta-analysis of the results of therapies for *H. pylori* infections often fail to provide useful information for clinicians.

Infectious diseases treatments are either successful (if they meet or exceed the prespecified criteria) or failures (if they do not). We previously suggested using ordered categories to gauge success with Grade A = >95% to Grade F or unacceptable = <85%, per protocol) treatment results [26]. Clinically, and for practical purposes, anti-*H. pylori* therapies should be judged as either good (e.g., >90 or 95%) or bad (e.g., <85%, per protocol). Ordered categories have an additional advantage over actual percentages as it prevents clinicians from averaging the results [e.g., if the average grade in one 6th grade class was A and in another B, they would be said to differ despite the fact that statistically using the actual numbers they might not (i.e., a B therapy can masquerade as an A but a B student would not be an A student when presenting their report card to their father)]. In the 13 trials covered in the recent meta-analysis, sequential generally, but not always, scored as a good therapy (i.e., >90% eradication or Grades A or B) and it was never inferior to triple therapy. In contrast, triple therapy uniformly scored as a bad therapy (Grade F). We believe that the summary recommendation and the editorial should have been to no longer use triple therapy as an empiric anti-*H. pylori* regimen (i.e., as first line or otherwise) [1]. The major cause of reduced effectiveness of triple and sequential therapy was the presence of resistance yet the authors of the editorial were possibly more concerned about location of the studies (i.e., “Most of the studies were conducted in Italy, and there is evidence that the efficacy of sequential therapy in Asia is more disappointing”) [1]. The site were a study is performed can best be considered a surrogate for a particular pattern of resistance and the pattern of resistance is the critical variable regarding whether the patients studied are similar to the ones he or she treats. In the United States and Europe (with the possible exception of Northern Europe) clarithromycin and metronidazole resistance patterns tends to be similar to Italy and one should expect sequential therapy to be a reasonable first choice therapy. However, because local conditions vary, post treatment confirmation of cure testing remains an important recommendation to ensue that what one is using is still effective (i.e., patterns of resistance can change rapidly) [3].

Role of meta-analysis in assessing *H. pylori* therapies

Meta-analysis does have a role to play in assessing *H. pylori* therapies. Before deciding on whether to perform a meta-analysis, one should first categorize regimens as good, bad, or variable and meta-analysis should only be used to compare good therapies (i.e., two or more therapies that both produce >90 or 95% success) so as to identify simpler (e.g., shorter, fewer less frequent administrations, different formulations, etc) or most cost effective .alternatives.

Summary

Sequential therapy is a good but typically not an excellent regimen (i.e., typically achieving a Grade B and not Grade A result) and theoretically it be improved [8]. Concomitant therapy uses the same components as sequential therapy but they are administered concomitantly rather than sequentially [27]. A recent head-to-head comparison of sequential and concomitant therapy showed that they were equivalent in the population studied [28]. Based on the effect on resistant strains there was also a suggestion that concomitant therapy may be more resistant to the effects of resistance but that hypothesis has not yet been tested in a high resistance population [28]. Since there was no obvious reason why amoxicillin was not

continued throughout the full sequential treatment regimen (to make a sequential-concomitant hybrid or simply hybrid therapy – Table 1) we tested whether that combination would achieved a Grade A result and it did (eradication rate PP of 99.1% (95% CI, 97.3%-100.0% with 117 subjects), in one recent trial [29]. Table 2 shows theoretically why hybrid therapy might be more effective than sequential therapy (i.e., patients with isolated clarithromycin resistance receive a triple therapy combination). Despite the excellent results of hybrid therapy in our initial trial and the theoretical reasons why it should be highly effective, enthusiasm should be tempered until the results are confirmed in other trials and in other regions. The fact that 10 day concomitant therapy appeared equivalent and not superior to 10 day sequential therapy suggests that initial dual component and its effect on eliminating the inoculum effect may play an important role in treatment success [28]. Bismuth is thought to work in a similar way [16].

Overall, optimization of common successful therapies is still needed as well as comparisons of those regimens in populations with different patterns of resistance. Such studies would allow the theoretical results shown in Table 2 and Figure 1 to become more precise and better predict outcomes. We continue support the advice that clinicians should use only what works locally and should continue to confirm cures so that one will be aware when resistance starts to undermine currently effective regimens [3]. Sequential therapy is overdue for being accepted for prime time.

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References

1. Moayyedi P, Malfertheiner P. Editorial: Sequential therapy for eradication of *Helicobacter pylori*: a new guiding light or a false dawn? Am J Gastroenterol. 2009; 104:3081–3083. [PubMed: 19956122]
2. 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. [PubMed: 19844205]
3. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. Gut. 2010; 59:1143–1153. [PubMed: 20525969]
4. 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. [PubMed: 10848654]
5. 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. [PubMed: 17566020]
6. 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. [PubMed: 20054285]
7. Graham DY. *Helicobacter pylori* Eradication Therapy Research: Ethical Issues and Description of Results. Clin Gastroenterol Hepatol. 2010 in press.
8. Graham DY, Lu H, Yamaoka Y. Therapy for *Helicobacter pylori* infection can be improved : sequential therapy and beyond. Drugs. 2008; 68:725–736. [PubMed: 18416582]

9. Zagari RM, Bianchi-Porro G, Fiocca R, et al. Comparison of 1 and 2 weeks of omeprazole, amoxicillin and clarithromycin treatment for *Helicobacter pylori* eradication: the HYPER Study. Gut. 2007; 56:475–479. [PubMed: 17028126]
10. Tanimura H, Kawano S, Kubo M, et al. Does *Helicobacter pylori* eradication depend on the period of amoxicillin treatment? A retrospective study. J Gastroenterol. 1998; 33:23–26. [PubMed: 9497217]
11. Furuta T, Shirai N, Takashima M, et al. Effects of genotypic differences in CYP2C19 status on cure rates for *Helicobacter pylori* infection by dual therapy with rabeprazole plus amoxicillin. Pharmacogenetics. 2001; 11:341–348. [PubMed: 11434512]
12. Furuta T, Graham DY. Pharmacological aspects of eradication therapy for *H. pylori* infection. Gastroenterol Clin North Am. In press.
13. Bazzoli F, Pozzato P. Therapy of H. pylori infection. J Physiol Pharmacol. 1997; 48 (Suppl 4):39–46. [PubMed: 9440054]
14. Shehada S, Srugo I, Shaoul R. Failure of sequential therapy to eradicate *Helicobacter pylori* in previously treated subjects. Helicobacter. 2007; 12:645–647. [PubMed: 18001409]
15. Graham DY. Efficient Identification and Evaluation of Effective *Helicobacter pylori* Therapies. Clin Gastroenterol Hepatol. 2009; 7:145–148. [PubMed: 19026766]
16. Graham DY. Antibiotic resistance in *Helicobacter pylori*: implications for therapy. Gastroenterology. 1998; 115:1272–1277. [PubMed: 9797384]
17. Graham DY, Shiotani A. New concepts of resistance in the treatment of *Helicobacter pylori* infections. Nat Clin Pract Gastroenterol Hepatol. 2008; 5:321–331. [PubMed: 18446147]
18. Noguchi N, Rimbara E, Kato A, et al. Detection of mixed clarithromycin-resistant and -susceptible *Helicobacter pylori* using nested PCR and direct sequencing of DNA extracted from faeces. J Med Microbiol. 2007; 56:1174–1180. [PubMed: 17761479]
19. Rimbara E, Noguchi N, Tanabe M, et al. Susceptibilities to clarithromycin, amoxycillin and metronidazole of *Helicobacter pylori* isolates from the antrum and corpus in Tokyo, Japan, 1995–2001. Clin Microbiol Infect. 2005; 11:307–311. [PubMed: 15760428]
20. Kim JJ, Kim JG, Kwon DH. Mixed-infection of antibiotic susceptible and resistant *Helicobacter pylori* isolates in a single patient and underestimation of antimicrobial susceptibility testing. Helicobacter. 2003; 8:202–206. [PubMed: 12752732]
21. Marais A, Monteiro L, Occhialini A, Pina, et al. Direct detection of *Helicobacter pylori* resistance to macrolides by a polymerase chain reaction/DNA enzyme immunoassay in gastric biopsy specimens. Gut. 1999; 44:463–467. [PubMed: 10075951]
22. Taylor NS, Fox JG, Akopyants NS, et al. Long-term colonization with single and multiple strains of *Helicobacter pylori* assessed by DNA fingerprinting. J Clin Microbiol. 1995; 33:918–923. [PubMed: 7790461]
23. Kim JM, Kim JS, Kim N, et al. Comparison of primary and secondary antimicrobial minimum inhibitory concentrations for *Helicobacter pylori* isolated from Korean patients. Int J Antimicrob Agents. 2006; 28:6–13. [PubMed: 16750904]
24. Wong BC, Wang WH, Berg DE, et al. High prevalence of mixed infections by *Helicobacter pylori* in Hong Kong: metronidazole sensitivity and overall genotype. Aliment Pharmacol Ther. 2001; 15:493–503. [PubMed: 11284778]
25. Versalovic J, Osato MS, Spakovsky K, et al. Point mutations in the 23S rRNA gene of *Helicobacter pylori* associated with different levels of clarithromycin resistance. J Antimicrob Chemother. 1997; 40:283–286. [PubMed: 9301997]
26. Graham DY, Lu H, Yamaoka Y. A report card to grade *Helicobacter pylori* therapy. Helicobacter. 2007; 12:275–278. [PubMed: 17669098]
27. Essa AS, Kramer JR, Graham DY, Treiber G. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing “concomitant therapy” versus triple therapy for *Helicobacter pylori* eradication. Helicobacter. 2009; 14:109–118. [PubMed: 19298338]
28. Wu DC, Hsu PI, Wu JY, et al. Sequential and concomitant therapy with 4 drugs are equally dffective for eradication of *H. pylori* infection. Clin Gastroenterol Hepatol. 2010; 8:36–41. [PubMed: 19804842]

29. Hsu PI, Wu DC, Wu JY, et al. Search for a grade A therapy for *Helicobacter pylori* infection: 14-day sequential or sequential-concomitant hybrid therapy. Gastroenterology. 2010; 138(Suppl 1):S-111.

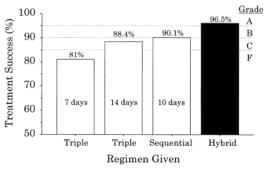

Figure 1. Results of a theoretical clinical trial evaluating different clarithromycin-containing *H. pylori* eradication regimens

Scenario: 100 patients per group from a population with a susceptibility pattern of 20% clarithromycin resistant, 20% metronidazole resistant and 0% amoxicillin resistant. Therefore among each 100 subjects 64 would be susceptible to all agents, 16 each would be clarithromycin resistant, 16 would be metronidazole resistant and 4 would be resistant to both clarithromycin and metronidazole (dual resistance). Treatment success is also graded using the Report Card scoring system [26].

Table 1

Our currently recommended *H. pylori* therapies for initial or second therapy

1. Recommended regimes for empiric therapy
Concomitant therapy: 4 drugs: Amoxicillin 1 g, clarithromycin 500 mg, tinidazole or metronidazole 500 mg, a PPI all given b.i.d. for 14 days (eg, PrevPac® or generics with an additional metronidazole or tinidazole 500 mg b.i.d. for 14 days). (generics are much cheaper)
Sequential therapy: Amoxicillin 1 g plus a PPI b.i.d. for 5 days, then clarithromycin 500 mg and tinidazole or metronidazole 500 mg b.i.d plus a PPI b.i.d. for 5 days to complete 10 days of total therapy
Sequential-concomitant hybrid therapy: Amoxicillin 1 g plus a PPI b.i.d. for 7 days, then amoxicillin 1 gm bid, plus clarithromycin 500 mg and tinidazole or metronidazole 500 mg b.i.d for 7 days to complete 14days.
Bismuth quadruple therapy: Bismuth subsalicylate 2 tabs q.i.d,, tetracycline HCl 500 mg q.i.d.(with meals and bedtime), metronidazole or tinidazole 500 mg, t.i.d. (with meals) and a PPI b.i.d. (or Helicac® with the addition of 3 extra 250 mg metronidazole to bring the dose up to acceptable plus a PPI given b.i.d. or Pylera® but extended to 14 days)
2. Acceptable regimes only for tailored therapy
Legacy triple therapy: 3 drugs including 2 of: amoxicillin 1 g, clarithromycin 500 mg, tinidazole or metronidazole 500 mg plus a PPI all given b.i.d. for 14 days
Fluoroquinolone-containing triple therapy: Once a day fluoroquinolone plus b.i.d. PPI and 1 gram amoxicillin for 14 days

Table 2

Example of the effects of resistance on outcome with clarithromycin-containing therapeutic regimens.

Resistant	Susceptible	Effective Rx	Cure rate
Triple 7 days			
None	Clari	PPI + C-A	95%
Clari	none	PPI + A	25%
Triple 14 days			
None	Clari	PPI + C-A	98%
Clair	None	PPI + A	50%
Sequential 10-14 days			
None	Clari, Met	PPI + C-M	98%
Met	Clari	PPI + C	90%
Clari	Met	PPI + M	75%**
Met-Clari	None	PPI +A	25%
Sequential-concomitant hybrid 14 days			
None	Clari-Met	PPI + C-M	98%
Met	Clari	PPI + C-A	95%
Clari	Met	PPI + M-A	95%
Met-Clari	None	PPI + A	50%

** This is an unexpectedly high result and may be unique to sequential therapy (see text for details).