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Helicobacter pylori therapy: a paradigm shift

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SUMMARY

Helicobacter pylori (*H. Pylori*) is a leading cause of gastroduodenal disease, including gastric cancer. *H. pylori* eradication therapies and their efficacy are summarized. A number of current treatment regimens will reliably yield >90% or 95% cure rates with susceptible strains. None has proven to be superior. We show how to predict the efficacy of a regimen in any population provided one knows the prevalence of antibiotic resistance. As with other infectious diseases, therapy should always be susceptibility-based. Susceptibility testing should be demanded. We provide recommendations for empiric therapies when the only option and describe how to distinguish studies providing misinformation from those providing reliable and interpretable data. When treated as an infectious disease, high *H. pylori* cure rates are relatively simple to reliably achieve.

Keywords

Helicobacter pylori; therapy; bismuth; proton pump inhibitor; clarithromycin; amoxicillin; metronidazole; levofloxacin; tetracycline

1. INTRODUCTION

H. pylori is an important human pathogen associated with and etiologically related to gastric cancer, mucosa-associated lymphoid tissue (MALT) lymphoma, and peptic ulcer disease as well as a variety of other conditions [1, 2]. Because gastric cancer is one of the most important causes of cancer deaths worldwide, efforts are underway in Japan, Taiwan, China, and Korea to implement gastric cancer eradication programs based on elimination of *H.*

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Declaration of interest

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pylori [2]. The consensus is now that all *H. pylori* infections detected should be eradicated unless there are compelling reasons [1].

Cure of *H. pylori* results in the rapid disappearance of the acute gastric mucosal inflammation, more gradual reduction of chronic inflammation, healing of peptic ulcers and prevention of ulcer recurrence and ulcer complications, and a reduction or elimination of the risk of gastric cancer [3, 4]. Because *H. pylori* associated gastric damage is progressive the ultimate effect of eradication depends on the degree of irreversible damage [1, 5-7].

2. Treatment of infectious diseases including *H. pylori*

As a general rule, therapy for an infectious disease starts with identification of potentially useful antimicrobials and is largely based on the results of susceptibility testing. Clinical trials are done to define the details of specific regimens including the drugs, formulations, route of administration, frequency of administration, duration, etc. The initial regimens may then be optimized by additional studies altering one or more elements such as dosing interval or treatment duration. For most common bacterial infections, very high cure rates are both achieved and expected. Following development of a new antimicrobials, clinical trials will be performed comparing the new regimen to standard-of-care regimens to ensure the new regimen is not inferior [8-10].

A fundamental principle of choosing therapy and the standard-of-care treatment for an infectious disease is to base the therapy on clinical trials performed with susceptibility testing. Therapy for an individual patient is then either chosen after susceptibility testing or if urgent therapy is required therapy is changed if susceptibility testing shows the original choice was poor. In diseases where resistance is infrequent, the standard-of-care regimen is often prescribed as empiric therapy. Culture also provides a method of monitoring the pattern of susceptibility in the population. If antimicrobial resistance begins to reduce the overall effectiveness of a regimen, the choice of therapy will change to an alternate regimen that maintains the desired high cure rate [11]. This practice pattern has been evident since increasing penicillin resistance resulted in changes in therapy for *Strep. pneumonia*, gonorrhea, syphilis, etc.

3. *H. pylori* therapy as an outlier among infectious diseases

The development of antimicrobial therapy for *H. pylori* has followed a unique course, possibly because development was largely done by gastroenterologists and gastroenterologists historically have had little prior experience in developing treatments for infectious diseases. *H. pylori* infection causes a chronic bacterial infection of the gastric mucosal surface. It is typically acquired in childhood and often is life-long. Because the disease has typically been present for decades there is essentially no indication that would require urgent therapy. The infection causes progressive mucosal damage leading to altered gastric physiology and may eventually destroy the normal mucosa which is replaced by metaplastic epithelia that cannot support the infection. Cure of the infection heals the inflammation, stops the progression of the damage and thus changes the natural history of the disease [12]. Treatment requires the use of antimicrobials to which the bacterium is

susceptible. *H. pylori* infection differs from many other common infections in that the organisms reside in many different niches and some, while inside the stomach, are functionally outside the body. The organisms can be found within gastric mucus, attached to surface cells, present deep within gastric pits, and can also invade gastric mucosal cells which may provide a sanctuary requiring systemic therapy [13, 14]. The physical characteristics, access to antibiotics, and pH of these niches vary. In addition, the acid environment of the stomach is hostile to the action of most antibiotics making most regimens more effective if anti-secretory drugs are given to increase the intragastric pH and reduce washout and dilution of the antimicrobials. Therapy is further complicated by the presence of a vast numbers of *H. pylori* within the infected stomach making it likely that subpopulations of resistant strains are present [14, 15]. The organisms also attach to the cell surface resulting in formation of a biofilm in which organisms display a significantly increased minimal inhibitory concentration toward antimicrobials [14, 16]. Effective therapy thus typically includes an antisecretory drug, several antimicrobials to reduce the chance of survival pre-existing resistant subpopulations, possibly a topical antimicrobial such as a bismuth salt, and sufficient duration to kill any dormant or infrequently replicating organisms (Table 1) [14, 17].

The development of new drug combinations has often ignored the painful lessons learned with the treatment of other infectious diseases and have continued to utilize a trial and error approach rather than use susceptibility to guide progress and form the basis for recommendations [18, 19].

4. History of *H. pylori* therapy

H. pylori therapy has a unique history. As noted above, the initial therapy and changes in therapy for common infectious diseases is almost universally susceptibility driven. First, antimicrobials to which the organism is susceptible are identified and tested in vivo. Successful drugs are then used to develop specific regimens (formulation, doses, dosing intervals, and duration), that will reliably cure approximately 100% of susceptible infections in adherent patients. Susceptibility testing becomes available worldwide and susceptibility-based therapy becomes the standard-of-care. New regimens are then compared to existing standards of care using non-inferiority trials. Finally, when resistance results in a decline in cure rates the standard-of-care be changed to maintain the desired high cure rates. The *H. pylori* story differs markedly from this scenario. *H. pylori* was shown to be susceptible to many antimicrobials in vitro [20]. In vitro susceptibility proved to be a poor predictor of in vivo effectiveness and it took several years to work out how to reliably achieve excellent results [21]. Initially, the infection proved easy to suppress but it rapidly recurred showing that obtaining an cure was more difficult. Cure was subsequently defined as absence of the infection 4 or more weeks after ending therapy. Regimens that would reliably produce high cure rates (i.e. 90% or greater) with susceptible infections generally required 2 or more antimicrobials plus an anti-secretory drug. The first universally available and highly promoted therapy was a triple therapy consisting of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin which was approved in the United States in 1997. It had a relatively short honeymoon before clarithromycin resistance began to increasingly undermine its effectiveness. By the early 2000's cure rates in Europe and the United States

had fallen below 85% and currently results as low as 50% are seen [22-25]. Pharmaceutical companies seemed to focus on convenience and marketing rather than on high cure rates such that even the original PPI, amoxicillin, clarithromycin triple therapies approved by the U.S. Food and Drug Administration (FDA) typically reported cure rates below 80% (Figure 1) [24-29]. At the same time, worldwide a cottage industry developed in which clinical trials tested and compared different drugs, doses and durations for *H. pylori* therapy while ignoring local patterns of susceptibility resulting in poor cure rates. Hundreds of studies were done involving thousands of patients. Most often the results were poor and even when they were acceptable (eg, 90% or greater cure rates), the general lack of susceptibility testing made them largely uninterpretable because the results were treatment population-specific, and not generalizable [23]. These poor results were typically related to widespread metronidazole resistance and to rapidly increasing clarithromycin resistance. New combinations of old regimens such as sequential therapy were developed and touted as superior to existing therapy [23]. Sequential therapy describes the addition of a third antimicrobial, metronidazole, to a modified clarithromycin triple therapy [30]. It appeared highly successful in Italy where success with clarithromycin triple therapy was no longer successful [30, 31]. However, failure to perform susceptibility testing did not allow investigators to understand the strengths and weaknesses of this regimen. It was subsequently compared to the poorly performing triple therapy in thousands of patients worldwide [32] and, as could have been predicted, it had high success in areas with a low prevalence of metronidazole or dual clarithromycin resistance and poor results wherever either were common. Regions with poor results were more common than those with good results and the regimen is now considered obsolete even by its inventors [32]. The trial and error approach remains common today and has been responsible for thousands of patients being involved in trials and comparisons in which poor outcomes were entirely predictable [33]. This phenomena was accompanied by many meta-analyses.

5. Meta-analyses or Shmeta-analyses?

Meta-analysis was introduced into medicine in order to allow one to group many small trials to identify overall effectiveness. Meta-analysis is defined by Wikipedia as "Conceptually, a meta-analysis uses a statistical approach to combine the results from multiple studies in an effort to increase power (over individual studies), improve estimates of the size of the effect and/or to resolve uncertainty when reports disagree". The method requires that the populations and trials be similar so they can be compared. Used properly meta-analyses can allow one to identify the better of two regimens for *H. pylori* eradication. However, most meta-analyses of therapies have been comparison of results in populations that differed remarkably in terms of susceptibility pattern. Thus, population-specific results were compared as if the populations and therapies were the same and thus producing erroneous conclusions (i.e., were Shmeta-analyses) [34]. There is no placebo response with *H. pylori* eradication therapy and the factors responsible for excellent and reduced effectiveness can almost always be reliably identified [35]. As such, a reasonable comparator for a clinical trial is how close the result comes to the desired 100% cured. Comparative trials should generally be designed to confirm non-inferiority in achieving excellent cure rates. Examples of meta-analysis based on erroneous principles are analyses done in populations in which

both regimens will reliably yield >90% cure rates (most often 95% or greater) in all regions of the world in patients with susceptible infection and who are adherent to the regimen (eg, a triple therapy containing 40 mg of omeprazole, 500 mg of clarithromycin, and 1,000 mg of amoxicillin, all given twice a day for 14 days) (Tables 2 and 3). Ten day sequential therapy (omeprazole 20 mg and amoxicillin 1,000 mg twice a day for 5 days followed by omeprazole 20 mg and clarithromycin 500 mg and metronidazole 500 mg all twice a day), when given to patients with susceptible infections will reliable achieve a cure rate of 90% to 94% (Table 2). An example of a Shmeta-analysis is an analysis of ten randomized control trials that enrolled 3,006 Italian adult patients and reported that the odds ratio (OR) for eradication of *H. pylori* with sequential therapy compared with triple therapy was 2.99 (95% confidence interval (CI): 2.47 – 3.62) [36]. The average cure rates were: sequential therapy = 90.9% and triple therapy = 75.4%, and the authors concluded that sequential therapy appeared to be better than triple therapy in the eradication of *H. pylori* [36]. Another example compared clarithromycin triple therapy with a PPI, amoxicillin and levofloxacin with bismuth quadruple therapy (a PPI, a bismuth salt, metronidazole and tetracycline) [37]. The doses and durations of the individual therapies varied. The authors concluded that their meta-analysis showed better results with levofloxacin than with the quadruple combination (OR= 1.80; 95% CI = 0.94–3.46). The cure rate were however unacceptable low with both (i.e., 81% vs. 70%; OR = 1.80; 95% CI = 0.94–3.46) [37]. The typical *H. pylori* therapy study still does not take into account the effects of resistance in the populations, or the doses, or durations of therapy.

Table 4 shows that there are a number of regimens that will reliable yield 90% cure rates (even 95% or greater) with susceptible infections in adherent patients. However, there are innumerable Shmeta-analyses of *H. pylori* therapy that report differences without discussing how such seemingly impossible results might have occurred. Probably no other infectious disease has so much published misinformation in the form of misleading conclusions and meta-analyses. It is safe to conclude that any clinical study that bases its conclusions on the results of studies in which susceptibility testing was not done, should be best ignored.

6. One solution

Almost every clinician in the world has access to a laboratory that will rapidly provide susceptibility testing for most if not all common pathogens they commonly encounter. *H. pylori* culture and susceptibility testing is not difficult and in addition many sites offer molecular testing for clarithromycin resistance using gastric biopsies, mucus, or even from stools [38]. The most common reasons offered for not testing *H. pylori* susceptibility is that culture is not available or is not reimbursed. These explanations are often presented as if they described insurmountable obstacles when they actually describe easily overcome problems. Governments would rather offer and pay for susceptibility testing than to retest and retreat a significant proportion of the population. In the presence of increasing resistance a susceptibility-based strategy has been shown to be cost effective [39]. Clearly, we clinicians must take the full blame for using excuses rather than attempting to solve the problem. Laboratories will provide what doctors want and demand. Culture can be done from gastric biopsies or brushing which can even be taken without endoscopy with a brush or string [40, 41]. Samples can then be placed in a simple transport medium and taken to the

laboratory or refrigerated and taken later [42]. Samples for culture can be processed immediately or frozen at −70 until processing. Clarithromycin susceptibility can even be assessed using stools. There is no reason susceptibility testing can be done locally other than we put up with it not being available at the price of poor cure rates. At a minimum, no clinical trial should be done or published without susceptibility data. As described above, the results of studies without susceptibility testing are population-specific and not generalizable. Since they can never answer the questions asked, they are by definition unethical as are studies comparing against a regimen known to be inferior [18, 19].

7. Recommended treatment regimens for *H. pylori*

The antimicrobials most widely used for *H. pylori* therapy include clarithromycin, amoxicillin, metronidazole, tetracycline, levofloxacin, furazolidone and bismuth. Worldwide resistance is often a problem with imidazoles (eg, metronidazole), macrolides (eg, clarithromycin) and fluoroquinolones (eg, levofloxacin).

We have divided the recommended treatment regimens into categories based first on a) whether susceptibility testing is available and the results known, b) as empiric therapies that one use based on local experience and patient history (Table 1), or c) as salvage therapies for patients who have failed two treatments with different drugs or from areas where multi-drug resistance is prevalent (Table 2). Finally, we discuss regimens that appear to be very useful but there are as yet insufficient data, those for which the details for optimum use have not yet been identified and, finally, future therapies that will probably come to dominate *H. pylori* treatment in the future (Table 3). The terms to describe conditions that produce optimal results are defined in Table 5. In some regions where CYP2C19 slow PPI metabolizers are common it may be possible to shorten the duration of therapy but we suggest that our recommendations be followed unless it has been confirmed that a change (eg, 7 vs. 10 days) reliably provides the same excellent outcome. Shorter duration has typically been used as a marketing tool and in many cases provides lower cure rates. The key word is "reliably".

8. Predicting the outcome in populations with different prevalences of resistance

To predict outcome of most therapies one must know the results with susceptible and resistant infection and the susceptibility result for the individual patient and/or the prevalence in the community. For triple therapies one can use the Hp-treatment nomogram to estimate the success rate for a population [43]. For an individual the success rate will be either that of a susceptible infection (eg, 97%) or a resistant infection (eg, 10%). The effect of any prevalence of resistance on the outcome of the population can be estimated from the plot (Figure 2) [43]. A 14-day triple therapy in a population with a 97% cure rate with susceptible infections and a 10% cure rate with 20% resistant infections would be expected to yield a per-protocol (PP) cure rate of approximately 80% (Figure 2) [43]. That result could also be easily calculated using the formula (% susceptible X # susceptible) + (% resistant X # resistant) which in this case equals 79.6%. Worldwide the cure rates with resistant strains (i.e., with twice a day PPI and amoxicillin component of triple therapy)

varies between 0 and 40% depending on the effectiveness of the PPI component in the PPI-amoxicillin dual therapy. Thus, the outcome with the prevalence of clarithromycin resistance of 20% could range between 77.6% to 85.6%, typically being highest in Asia where CYP2C19 slow metabolizers are most common. The regional variation in resistance and in PPI effectiveness is another reason why uncritical grouping of studies in meta-analyses may produce misleading results.

For those mathematically inclined the details of how to choose a therapy is well described in the recent literature which also contain appropriate formulas and a decision model and sensitivity analysis based on the effectiveness in relation to antibiotic susceptibility [11, 44]. For susceptible infection one can choose an effective regimen from Table 1. For patients in regions where susceptibility is unknown, one must rely on population data and on the history of antimicrobial use by the patient. Ideally, choice of therapy should be susceptibility-based. The lack of susceptibility testing in the face of increased resistance has resulted in increased use of 4-drug regimes for empiric therapy (Table 1). The general rule is to choose from those regimens that are proven to be successful locally. The two empiric therapies that are effective in most regions are bismuth quadruple therapy and concomitant therapy (Table 1) [11, 33].

9. Bismuth quadruple therapy

The original highly successful therapy for *H. pylori* eradication was developed by Borody et al. in 1989 and consisted of bismuth, metronidazole, and tetracycline [45]. Because of reduced effectiveness in the presence of metronidazole resistance, a PPI was added and the duration of therapy extended which maintained its effectiveness despite metronidazole resistance [17, 46]. Bismuth quadruple therapy consists of bismuth tablets (2 tablets 4 times daily), tetracycline 500 mg 4 times daily, metronidazole 500 mg 3 times daily (in Europe or Asia as 400 mg 4 times daily) and a PPI, twice daily for 14 days [17, 46]. Studies from China have shown that it is possible to reduce the bismuth and tetracycline to twice a day [17, 47]. In the absence of metronidazole resistance it is possible to also shorten the duration of therapy to 7 or 10 days and possibly reduce the dose of metronidazole. In the absence of metronidazole resistance one would always prefer metronidazole triple therapy because of its greater patient acceptability. In the presence of metronidazole resistance, a metronidazole dose of 1,500 or 1,600 mg is needed along with a duration of 14 days for best results [17]. It remains unknown if 12 day therapy is similarly effective as head-to-head comparisons of 12 and 14 day therapies have not been done. Bismuth quadruple therapy is associated with a high incidence of side effects such that patient education is important if one wants to achieve a high proportion of adherent subjects. A combination capsule containing bismuth subcitrate 140 mg, metronidazole 125 mg, and tetracycline hydrochloride125 mg (PYLERA) has become increasing available. It is packaged for 10 day therapy instead of the preferred 14 day therapy. In the United States 10 day therapy costs $400 U.S. ($600 for 14 day therapy), whereas in Italy the cost for 10 day therapy is € 64.00. There are as yet no data that the prepackaged products produce improved adherence or outcome. In China where bismuth quadruple therapy uses twice a day bismuth and tetracycline the number of tablets is less than with the prepackaged products [47].

Because of the propensity for side effects, the primary indications for bismuth quadruple therapy are penicillin allergy and suspected metronidazole resistance and clarithromycin resistance (i.e., as a second line therapy). As noted, 10 day therapy is sufficient in the presence of metronidazole susceptibility whereas 14 day therapy is recommended in the presence of metronidazole resistance. In the presence of metronidazole susceptibility and no penicillin allergy, 14 day metronidazole-amoxicillin triple therapy would be preferred.

The worldwide shortage of tetracycline as resulted in many pharmacies attempting to shift to doxycycline [48]. There is a suggestion that high dose doxycycline therapy might be effective but this approach has not been tested in relation to metronidazole resistance [49]. It is our experience, doxycycline provides poor cure rates when substituted of tetracycline in regions with metronidazole resistance and we suggest that it be avoided unless new susceptibility-based data shows that it can be used effectively in the presence of metronidazole resistance (discussed in detail in reference [46]).

10. Concomitant therapy

Concomitant therapy can be considered as fundamentally the same as giving clarithromycin and metronidazole triple therapy simultaneously. Adherent subjects with clarithromycin susceptible infections will receive 14 day clarithromycin triple therapy. Those with metronidazole susceptible infections will receive 14 day metronidazole triple therapy. Each of these subgroups will achieve 95% or greater cures. Those with clarithromycin-metronidazole dual resistance will effectively receive only PPI amoxicillin dual therapy and achieve whatever the cure rate is for that regimen in that population (range 0% to 40%, in the U.S. 0% to 20%) [2]. One can estimate the proportion with dual resistance in any population as the proportion with clarithromycin resistance times the proportion with metronidazole resistance [2]. In most populations of western countries dual resistance will be less than 5%. However, if both clarithromycin and metronidazole have been used (eg, in sequential therapy) dual resistance would be likely. For practical purposes one can consider the results with concomitant as binary [susceptible or resistant, (i.e., either clarithromycin or metronidazole susceptible or as dual clarithromycin-metronidazole resistant) and calculate the expected cure rate using a readily available formula, web site, or *H. pylori* therapy nomogram [43].

Although clarithromycin-containing triple therapy has generally become obsolete, convenience packs are still widely available (in the U.S. as Prevpac) and these can be easily transformed into concomitant therapy by providing a second prescription for 500 mg of metronidazole or tinidazole to be taken 2 times daily. Resistance to clarithromycin, metronidazole, levofloxacin, and rifabutin is essentially all-or-non such that these drugs essentially drop out and the patient in effect receives only the remaining drugs, in most cases the PPI and amoxicillin. However metronidazole resistance can be overcome by increasing the dose to 1,500 mg or more and increasing the duration of therapy. Amoxicillin resistance remains rare and can generally be ignored. The effectiveness of regimens is affected by factors that change antisecretory activity. Factors that improve antisecretory drug effectiveness include corpus gastritis and slow PPI metabolism. Factors that reduce the antisecretory activity are those that increase acidity such as smoking, or rapid PPI

metabolism. This is especially evident when examining the results in Western vs. Asian populations. Western populations are more likely to have a high proportion of rapid PPI metabolizers and a low prevalence of corpus gastritis; Asian populations are the opposite.

11. Salvage therapies

Salvage therapies are defined as those used in patients who have failed two prior usually high cure rate therapies with different antibiotics. Salvage regimens typically use drugs that are infrequently used and thus resistance is rare (i.e., furazolidone and rifabutin) and those in which resistance rarely develops such as amoxicillin and tetracycline (Table 2). Furazolidone is unavailable in most countries, but where it is available, the results are typically excellent provided that furazolidone is given at the recommended dose (eg, 100 mg three times daily) and duration (eg, 14 days) [50]. In China there has been good success with twice a day bismuth [50]. The 4 drug furazolidone-containing regimen can use either tetracycline (if available) or amoxicillin if not (Table 2). In our experience, failures are almost non-existent but side effects are common with many patients having difficulty finishing the regimen. Even in those patients cure is expected. There are a few papers cautioning against furazolidone use and suggesting that it is a proven carcinogen. Metronidazole is a class I (definite human carcinogen). In contrast, furazolidone is classified as a class III agent meaning there are not data supporting that it is carcinogenic for humans [51]. The authors of those negative papers may have possibly misinterpreted the meaning of a class III carcinogen.

12. Rifabutin-containing regimens

Rifabutin is rarely used except for difficult cases of tuberculosis or atypical tuberculosis. Therapy for 7 and 10 days has typically provided low cure rates [52, 53]. Borody et al. and Lim et al. [54, 55] had better results with higher doses of PPI and amoxicillin given three times daily for 12 and 7 days respectively. Recently, two pilot non-randomized studies evaluated 10 day twice a day rifabutin triple therapy and separately a 10 day rifabutin quadruple therapy in which bismuth subcitrate was added twice a day. In this quadruple therapy, the cure rate without the addition of bismuth was poor (66.7%) but increased to 96.6% (28/29) with the addition of bismuth [56]. At this time one can only conclude that the details for producing a reliable rifabutin-containing therapy are still unknown.

13. High dose PPI-amoxicillin dual therapy

Dual PPI-amoxicillin therapy was introduced in 1989 and has been extensively studied (reviewed in reference [17]). The PPIs (eg, omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole and dexlansoprazole) block acid secretion by irreversibly binding to and inhibiting the hydrogen-potassium ATPase pump that resides on the luminal surface of the parietal cell membrane. PPIs are weak bases that are concentrated in the acidic compartments of the parietal cell. The inactive prodrug is activated by the acid environment and forms an irreversible bond with a cysteine residue on the H-K-ATPase pump that blocks the enzyme. The drugs have a short period to block the enzyme activity (approximately 90 minutes) after which, newly manufactured pumps are no longer blocked. In order to almost

completely inhibit acid secretion, it is necessary to maintain a blood level of the PPI which requires a continuous infusion [57].

H. pylori exhibit phenotypic antimicrobial resistance characterized by the presence of organisms that survive during treatment because they remain in a state of non-replication [14, 58]. *H. pylori* only replicate when the pH is high such that increasing the pH to approximately 6 will trigger the bacteria to enter in a replicative state and become phenotypically susceptible to antibiotics effective with replicating organisms. This is the basis of high-dose PPI frequently administered PPI and amoxicillin therapy [59]. The keys to successful dual therapy are still unclear but the available data points to the importance of maintaining the intragastric pH at 6 or greater and probably maintaining amoxicillin blood levels above the minimal inhibitory concentration throughout the treatment period (discussed in detail in ref [17]. With a few exceptions, treatment has only been reliably successful in areas where CYP2C19 slow PPI metabolizers are common and the PPI and amoxicillin are given approximately every 6 hours. In western countries the results have often been disappointing especially in those who have failed therapy previously. We believe this process selects for the group of patients in whom obtaining a high intragastric pH is difficult. Our experience is that when used as a salvage therapy many if not most in the United States fail dual therapy even when given as high dose PPI and amoxicillin every 6 hours.

14. Emerging therapy: vonoprazan

This is a new class of anti-secretory drugs, the potassium competitive acid blockers, that bind and block the acid pump for more than 24 hours [60]. This drug will allow its minimal inhibitory concentration. The doses used currently as an adjuvant to clarithromycin triple therapy (20 mg twice a day) when given with amoxicillin 750 mg twice a day in those with clarithromycin resistant strains only cured 82% suggesting that either the pH response was insufficient, the dosing of amoxicillin, and/or the duration were inadequate to achieve good or excellent results [61]. We however expect that future studies with this combination will identify effective combinations and radically change *H. pylori* therapy for those who can also take penicillins.

15. Expert Commentary

Generally, *H. pylori* therapy has been developed as if were simply another gastrointestinal disease such as constipation whose cause was unknown and in which the placebo response to treatment requires a comparator therapy for analysis. Resistance to commonly used antimicrobials has resulted in increasing poor cure rates leading to clinical trials comparing treatment regimens most often without regard to the key role of antimicrobial resistance on outcome. Comparative studies have confirmed that, in the presence of a high prevalence of antimicrobial resistance, susceptibility-based therapy will always be superior to empiric therapy. A number of treatment regimens are now available that will reliably cure at least 90% if not 95% of *H. pylori* infections with susceptible organisms. The therapy of *H. pylori* is changing from one based on trial-and-error to becoming susceptibility-based. Further

change will require that scientific journals embrace the concept that *H. pylori* treatment trials should be judged using the same standards as for other infectious diseases.

16. Five-year view

The newly described ability to reliably and easily maintain the intragastric pH at 6 or more during therapy should revolutionize and simplify therapy and ensure high cure rates. Until that occurs worldwide, we will need more laboratories to offer *H. pylori* susceptibility testing which in turn will require that clinicians demand it. We predict improved molecular testing using stool and an extension of molecular testing to more antimicrobials. We also predict that scientific journals will stop accepting clinical trials without accompanying susceptible data as well as comparative studies in which a known inferior regimen (eg because of high local resistance) is compared to one uninfluenced by that problem. Studies without susceptibility data and comparisons with assured outcomes lack clinical equipoise, are likely unethical, and this should neither be done nor published. Eradication of *H. pylori* to essentially eliminate gastric cancer programs will become widespread.

17. Key Issues

- *H. pylori* infections should be thought of as similar to other common infectious diseases. Therapy should based on susceptibility and cure rates of >90% expected.
- There are a number of treatment regimens that will reliably yield >90% or 95% cure rates with susceptible strains. None has proven to be superior.
- Comparative studies should be as non-inferiority trials.
- No clinical trial should be done without assessing susceptibility. Results should be presented separately for susceptible and resistant infection.
- Studies without susceptibility data yield results restricted to the population studied and are thus neither generalizable nor ethical.
- Comparative trials in populations with a high prevalence of resistance testing actually combine results from two subpopulations (those with susceptible and those with resistant infections) of unknown size and are thus neither interpretable nor ethical.
- Because of the high rates of resistance, triple therapies containing clarithromycin, a fluoroquinolone, or nitroimidazole should not be prescribed as empiric therapy unless proven to be highly effective locally.
- Use recommended doses and durations of therapy unless it has been proven that lower doses or shorter durations reliably produce eradication rates equivalent to those recommended here.

References

Reference annotations

* Of interest

** Of considerable interest

1. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut. 2015; 64:1353–1367. [PubMed: 26187502] **This is an important recent consensus of *H. pylori* gastritis and the relation of *H. pylori* to other diseases. It defines *H. pylori* as an infectious diseases and provides the evidence that all *H. pylori* infections should be treated unless there are compelling reasons.
2. Graham DY. *Helicobacter pylori* update: Gastric cancer, reliable therapy, and possible benefits. Gastroenterology. 2015; 148:719–731. [PubMed: 25655557] *Up to date review of the role of *H. pylori* in gastric cancer, *H. pylori* therapy, and review of its possible role in myocardial infarction, gastroesophageal reflux disease, childhood asthma, and obesity.
3. Genta RM, Lew GM, Graham DY. Changes in gastric mucosa following eradication of *Helicobacter pylori*. Mod Pathol. 1993; 6:281–289. [PubMed: 8346176]
4. Sung JJ, Lin SR, Ching JY, et al. Atrophy and intestinal metaplasia one year after cure of *H. pylori* infection: a prospective, randomized study. Gastroenterology. 2000; 119:7–14. [PubMed: 10889149]
5. De Bernard M, Josenhans C. Pathogenesis of *Helicobacter pylori* infection. Helicobacter. 2014; 19(Suppl 1):11–18. [PubMed: 25167940]
6. Axon A. *Helicobacter pylori* and public health. Helicobacter. 2014; 19(Suppl 1):68–73. [PubMed: 25167948]
7. Sgouras DN, Trang TT, Yamaoka Y. Pathogenesis of *Helicobacter pylori* infection. Helicobacter. 2015; 20(Suppl 1):8–16. [PubMed: 26372819]
8. Geisler WM, Uniyal A, Lee JY, et al. Azithromycin versus doxycycline for urogenital *Chlamydia trachomatis* infection. N Engl J Med. 2015; 373:2512–2521. [PubMed: 26699167]
9. Ghanem KG, Erbelding EJ, Cheng WW, et al. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. Clin Infect Dis. 2006; 42:e45–e49. [PubMed: 16477545]
10. Riedner G, Rusizoka M, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. N Engl J Med. 2005; 353:1236–1244. [PubMed: 16177249]
11. Wu JY, Liou JM, Graham DY. Evidence-based recommendations for successful *Helicobacter pylori* treatment. Expert Rev Gastroenterol Hepatol. 2014; 8:21–28. [PubMed: 24410470]
12. Shiotani A, Cen P, Graham DY. Eradication of gastric cancer is now both possible and practical. Semin Cancer Biol. 2013; 23:492–501. [PubMed: 23876852]
13. Suerbaum S, Michetti P. *Helicobacter pylori* infection. N Engl J Med. 2002; 347:1175–1186. [PubMed: 12374879]
14. 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]
15. Graham DY. Antibiotic resistance in *Helicobacter pylori*: implications for therapy. Gastroenterology. 1998; 115:1272–1277. [PubMed: 9797384]
16. Yonezawa H, Osaki T, Kamiya S. Biofilm Formation by *Helicobacter pylori* and its involvement for antibiotic resistance. Biomed Res Int. 2015; 2015:914791. [PubMed: 26078970]
17. Dore MP, Lu H, Graham DY. Role of bismuth in improving *Helicobacter pylori* eradication with triple therapy. Gut. 2016 (in press). *Excellent review of the use of bismuth in *H. pylori* therapy and of PPI-amoxicillin dual therapy.
18. Graham DY. *Helicobacter pylori* eradication therapy research: Ethical issues and description of results. Clin Gastroenterol Hepatol. 2010; 8:1032–1036. [PubMed: 20656062]
19. Graham DY. Editorial - Avoiding unethical *Helicobacter pylori* clinical trials: Susceptibility-based studies and probiotics as adjuvants. Helicobacter. 2015; 20:321–325. [PubMed: 26123529]
20. Goodwin CS, Worsley BW. Microbiology of *Helicobacter pylori*. Gastroenterol Clin North Am. 1993; 22:5–19. [PubMed: 8449570]
21. Borsch, GM.; Graham, DY. Helicobacter pylori. In: Collen, MJ.; Benjamin, SB., editors. Pharmacology of Peptic Ulcer Disease. Vol. Handbook of Experimental Pharmacology Vol 99. Springer-Verlag; Berlin: 1991. p. 107-148.

22. Buzas GM, Jozan J. First-line eradication of *H pylori* infection in Europe: a meta-analysis based on congress abstracts, 1997-2004. World J Gastroenterol. 2006; 12:5311–5319. [PubMed: 16981260] *Review showing how triple therapy has been failing in Europe since the early 2000's.
23. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. Gut. 2010; 59:1143–1153. [PubMed: 20525969]
24. Yamaoka Y, Graham DY, Lu H. Should triple therapy for *Helicobacter pylori* infection be abandoned as no longer effective? US Gastroenterology. 2008; 4:65–67. *Review showing how triple therapy has been failing worldwide since the early 2000's.
25. Graham DY, Lu H, Yamaoka Y. A report card to grade *Helicobacter pylori* therapy. Helicobacter. 2007; 12:275–278. [PubMed: 17669098]
26. Bochenek WJ, Peters S, Fraga PD, et al. Eradication of *Helicobacter pylori* by 7-day triple-therapy regimens combining pantoprazole with clarithromycin, metronidazole, or amoxicillin in patients with peptic ulcer disease: Results of two double-blind, randomized studies. Helicobacter. 2003; 8:626–642. [PubMed: 14632678]
27. Fennerty MB, Kovacs TO, Krause R, et al. A comparison of 10 and 14 days of lansoprazole triple therapy for eradication of *Helicobacter pylori*. Arch Intern Med. 1998; 158:1651–1656. [PubMed: 9701099]
28. Vakil N, Lanza F, Schwartz H, et al. Seven-day therapy for *Helicobacter pylori* in the United States. Aliment Pharmacol Ther. 2004; 20:99–107. [PubMed: 15225176]
29. Laine L, Frantz JE, Baker A, et al. A United States multicentre trial of dual and proton pump inhibitor-based triple therapies for *Helicobacter pylori*. Aliment Pharmacol Ther. 1997; 11:913–917. [PubMed: 9354200]
30. Zullo A, Vaira D, Vakil N, et al. High eradication rates of *Helicobacter pylori* with a new sequential treatment. Aliment Pharmacol Ther. 2003; 17:719–726. [PubMed: 12641522]
31. Vaira D, Zullo A, Vakil N, et al. Sequential therapy versus standard triple-drug therapy for *Helicobacter pylori* eradication: a randomized trial. Ann Intern Med. 2007; 146:556–563. [PubMed: 17438314]
32. Gatta L, Vakil N, Vaira D, et al. Global eradication rates for *Helicobacter pylori* infection: systematic review and meta-analysis of sequential therapy. BMJ. 2013; 347:f4587. [PubMed: 23926315]
33. Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: Evidence-based medicine rather than medicine-based evidence. Clin Gastroenterol Hepatol. 2014; 12:177–186. [PubMed: 23751282] **Comprehensive analysis of the status of *H. pylori* therapy and suggestions for individualize regimens for the single patient on the base of previous use of antibiotics and estimation of risk resistant infection.
34. Shapiro S. Meta-analysis/Shmeta-analysis. Am J Epidemiol. 1994; 140:771–778. [PubMed: 7977286]
35. Graham DY, Dore MP. *Helicobacter pylori* therapy demystified. Helicobacter. 2011; 16:343–345. [PubMed: 21923679]
36. 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]
37. Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. Aliment Pharmacol Ther. 2006; 23:35–44. [PubMed: 16393278]
38. Megraud F, Benejat L, Ontsira Ngoyi EN, et al. Molecular approaches to identify *Helicobacter pylori* antimicrobial resistance. Gastroenterol Clin North Am. 2015; 44:577–596. [PubMed: 26314669] *Recent review of molecular methods to determine *H. pylori* resistance to macrolides, fluoroquinolones, tetracycline and rifampin.
39. Cosme A, Montes M, Martos M, Gil I, et al. Usefulness of antimicrobial susceptibility in the eradication of *Helicobacter pylori*. Clin Microbiol Infect. 2013; 19:379–383. [PubMed: 22512623]
40. Graham DY, Kudo M, Reddy R, et al. Practical rapid, minimally invasive, reliable nonendoscopic method to obtain *Helicobacter pylori* for culture. Helicobacter. 2005; 10:1–3. [PubMed: 15691309]

41. Perez-Trallero E, Montes M, Alcorta M, et al. Non-endoscopic method to obtain *Helicobacter pylori* for culture. Lancet. 1995; 345:622–623. [PubMed: 7898181]
42. Han SW, Flamm R, Hachem CY, Kim HY, et al. Transport and storage of *Helicobacter pylori* from gastric mucosal biopsies and clinical isolates. Eur J Clin Microbiol Infect Dis. 1995; 14:349–352. [PubMed: 7649201]
43. Graham DY. Hp-normogram (normo-graham) for assessing the outcome of *H. pylori* therapy: Effect of resistance, duration, and CYP2C19 genotype. Helicobacter. 2016; 21:85–90. [PubMed: 26612515] ** The study illustrates how to use a nomogram to reliably predict the outcome of *H. pylori* treatment regimens in the presence of resistant infections.
44. Liou JM, Chen CC, Chen MJ, et al. Sequential versus triple therapy for the first-line treatment of *Helicobacter pylori*: a multicentre, open-label, randomized trial. Lancet. 2013; 381:205–213. [PubMed: 23158886]
45. Borody TJ, Cole P, Noonan S, et al. Recurrence of duodenal ulcer and *Campylobacter pylori* infection after eradication. Med J Aust. 1989; 151:431–435. [PubMed: 2687668]
46. Graham DY, Lee SY. How to effectively use bismuth quadruple therapy: The good, the bad, and the ugly. Gastroenterol Clin North Am. 2015; 44:537–563. [PubMed: 26314667] *The study reviews the details of how to use bismuth quadruple therapy and explains why studies vary.
47. Zhang W, Chen Q, Liang X, et al. Bismuth, lansoprazole, amoxicillin and metronidazole or clarithromycin as first-line *Helicobacter pylori* therapy. Gut. 2015; 64:1715–1720. [PubMed: 26338726]
48. Borody TJ, George LL, Brandl S, et al. *Helicobacter pylori* eradication with doxycycline-metronidazole-bismuth subcitrate triple therapy. Scand J Gastroenterol. 1992; 27:281–284. [PubMed: 1589705]
49. Ciccaglione A, Cellini L, Grossi L, et al. A triple and quadruple therapy with doxycycline and bismuth for first-line treatment of *Helicobacter pylori* infection: a pilot study. Helicobacter. 2016 (in press).
50. Lu H, Zhang W, Graham DY. Bismuth-containing quadruple therapy for *Helicobacter pylori*: lessons from China. Eur J Gastroenterol Hepatol. 2013; 25:1134–1140. [PubMed: 23778309]
51. 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. [PubMed: 22249084]
52. Gisbert JP, Castro-Fernandez M, Perez-Aisa A, et al. Fourth-line rescue therapy with rifabutin in patients with three *Helicobacter pylori* eradication failures. Aliment Pharmacol Ther. 2012; 35:941–947. [PubMed: 22372560]
53. Gisbert JP, Calvet X. Review article: rifabutin in the treatment of refractory *Helicobacter pylori* infection. Aliment Pharmacol Ther. 2012; 35:209–221. [PubMed: 22129228]
54. 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. [PubMed: 16441468]
55. Lim HC, Lee YJ, An B, et al. Rifabutin-based high-dose proton-pump inhibitor and amoxicillin triple regimen as the rescue treatment for *Helicobacter pylori*. Helicobacter. 2014
56. Ciccaglione AF, Tavani R, Grossi L, et al. Rifabutin containing triple therapy and rifabutin with bismuth Containing quadruple therapy for third-line treatment of *Helicobacter pylori* infection: Two pilot studies. Helicobacter. 2016
57. Julapalli VR, Graham DY. Appropriate use of intravenous proton pump inhibitors in the management of bleeding peptic ulcer. Dig Dis Sci. 2005; 50:1185–1193. [PubMed: 16047458]
58. Scott D, Weeks D, Melchers K, et al. The life and death of *Helicobacter pylori*. Gut. 1998; 43(Suppl 1):S56–S60. [PubMed: 9764042]
59. Furuta T, Graham DY. Pharmacologic aspects of eradication therapy for *Helicobacter pylori* Infection. Gastroenterol Clin North Am. 2010; 39:465–480. [PubMed: 20951912]
60. Sakurai Y, Nishimura A, Kennedy G, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising TAK-438 (Vonoprazan) doses in healthy male Japanese/non-Japanese subjects. Clin Transl Gastroenterol. 2015; 6:e94. [PubMed: 26111126]

61. Murakami K, Sakurai Y, Shiino M, et al. Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: a phase III, randomised, double-blind study. Gut. 2016 (in press). **This is the first clinical trial of vonoprazan, a potassium-competitive acid blocker, as a component of *H. pylori* eradication therapy in a randomised, double-blind, multicentre study.

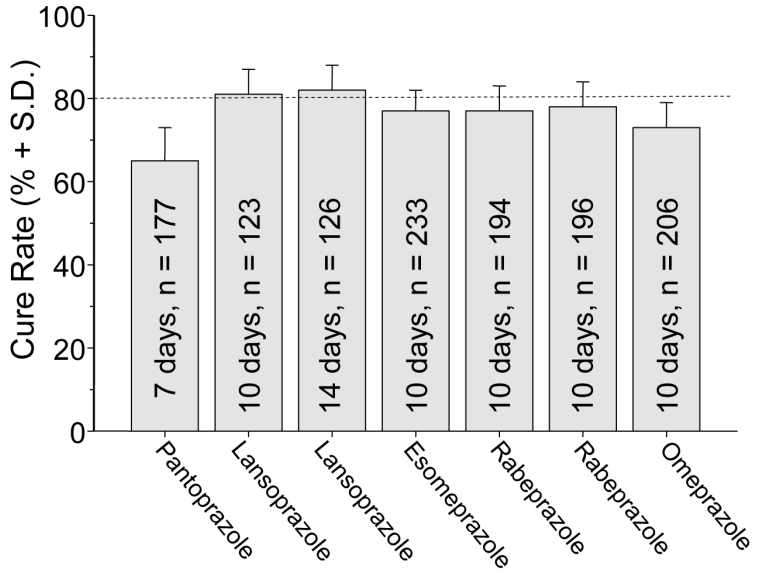

Figure 1.

Intention to treat cure rates and standard deviation reported for the clinical trials done to obtain US Food and Drug Administration approval for PPI, clarithromycin, amoxicillin triple in the United States [26-29].

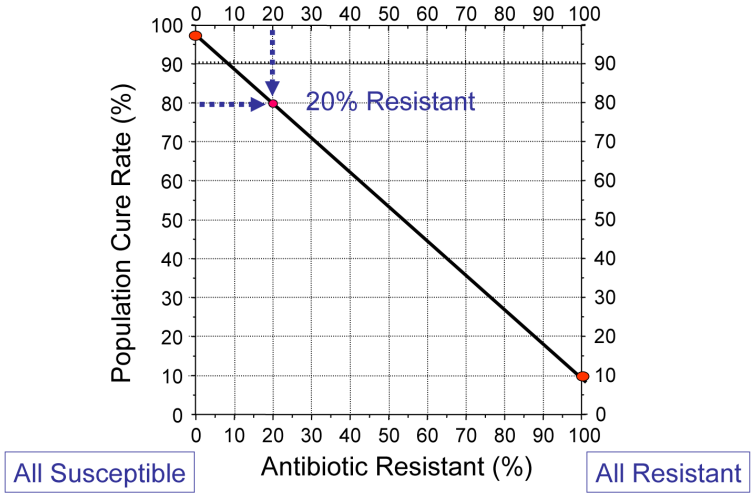

Figure 2.

H. pylori nomogram. This nomogram plots the cure rate with susceptible infections on the left vertical axis and those with resistant infections on the right vertical axis. The proportion with resistance is shown on the horizontal axis [43]. The cure rates with 100% susceptible and 100% clarithromycin resistant are connected with a line allowing one to visualize the population cure rates for any prevalence of resistance. This plot shows the cure rates with a 14 day PPI, clarithromycin, amoxicillin triple therapy in a western population in relation to the prevalence of clarithromycin resistance. It also illustrates the expected cure rate, per protocol, expected with a prevalence of clarithromycin resistance of 20%.

Table 1

Recommended treatment regimens for *Helicobacter pylori* eradication

Treatment	Drugs, dosages and duration
Susceptibility-based	**No drug allergies**
Clarithromycin Triple Therapy (susceptible to clarithromycin)	Amoxicillin (1 g) and clarithromycin (500 mg) plus a PPI all given twice daily for 14 days (40 mg esomeprazole equivalent per dose)
Metronidazole Triple Therapy (susceptible to metronidazole)	Amoxicillin (1 g) and tinidazole (500 mg) or metronidazole (500 mg) plus a PPI all given twice daily for 14 days (40 mg esomeprazole equivalent per dose)
Fluoroquinolone Triple Therapy (susceptible to fluoroquinolones)	Fluoroquinolone (e.g. levofloxacin 500 mg once daily), plus a PPI and amoxicillin 1 g twice daily for 14 days (40 mg esomeprazole equivalent per dose)
Susceptibility-based	**Allergic to penicillin**
Susceptible to clarithromycin and metronidazole	Clarithromycin (500 mg), and tinidazole (500 mg) or metronidazole (500 mg) plus a PPI (40 mg esomeprazole equivalent per dose) all given twice daily for 14 days
Resistant to clarithromycin and/or metronidazole	Bismuth quadruple therapy (see empiric therapies)
Empiric therapies	**Susceptibility testing unavailable**
Concomitant therapy	Amoxicillin (1 g), clarithromycin (500 mg), and tinidazole (500 mg) or metronidazole (500 mg) plus a PPI (40 mg esomeprazole equivalent per dose) all given twice daily for 14 days
Bismuth quadruple therapy	Bismuth subsalicylate or bismuth subcitrate 2 tablets and tetracycline hydrochloride (500 mg) both four times daily with meals and at bedtime plus metronidazole/tinidazole (500 mg) three times daily with meals and a PPI twice daily for 14 days (see text).
Prepackaged bismuth quadruple therapy	PYLERA for 14 days; add a PPI b.i.d. (40 mg esomeprazole equivalent per dose)

Preferred PPI's: Esomeprazole 40 mg, rabeprazole 20 mg. Vonoprazan can substitute for the PPI

Table 2

Recommended salvage therapy regimens for *Helicobacter pylori* eradication

Treatment	Drugs, dosages and duration
Empiric salvage therapy	**(After 2 or more failures with different drugs)**
Furazolidone quadruple therapy with tetracycline	Bismuth subsalicylate or bismuth subcitrate 2 tablets and tetracycline hydrochloride (500 mg) both four times daily with meals and at bedtime plus furazolidone 100 mg t.i.d., with meals and PPI twice daily for 14 days
Furazolidone quadruple therapy with amoxicillin	Bismuth subsalicylate or bismuth subcitrate 2 four times daily with meals and at bedtime plus furazolidone 100 mg and amoxicillin 1 gram t.i.d., with meals plus a PPI twice daily for 14 days
Rifabutin therapies	See Table 3.
High dose PPI-amoxicillin dual therapy	PPI (e.g. rabeprazole 20 mg, esomeprazole 40 mg) plus amoxicillin (500 - 750 mg) all four times daily at approximately 6 h intervals for 14 days (can use 8 hour interval at night) (effective for CYP2C19 poor metabolizers - see text)

Preferred PPI's: Esomeprazole 40 mg, rabeprazole 20 mg.

Table 3

New likely effective regimens, Future regimens and Obsolete regimens

Treatment	Drugs, dosages and duration
Empiric likely effective regimens	
Hybrid (sequential–concomitant) therapy	Amoxicillin (1 g) plus a PPI twice daily (40 mg esomeprazole equivalent per dose) for 7 days, followed by amoxicillin (1 g), clarithromycin (500 mg) and tinidazole (500 mg) or metronidazole (500 mg) for a further 7 days (total 14 days)
New bismuth quadruple therapy (amoxicillin replaces tetracycline)	Bismuth 2 tablets 2 to 4 times daily with meals and at bedtime plus metronidazole/tinidazole (500 mg) three times daily (or 400 mg four times daily) with meals and amoxicillin 1 gm three times daily along with a PPI twice daily for 14 days [44].
Rifabutin triple therapy	Rifabutin (150 mg once or twice daily), amoxicillin (1.5 g) and esomeprazole 40 mg (or an equivalent PPI) every 8 hours for 14 days.
Rifabutin bismuth therapy	Rifabutin 150 mg, amoxicillin 1 gram, bismuth subcitrate or subsalicylate 2 tablets, a PPI all twice daily for 14 days
Future Regimens	
Vonoprazan-amoxicillin dual therapy	Vonoprazan, a potassium competitive acid blocker, is potentially more effective than a current PPIs for maintaining intragastric pH at 6 or above. 7 day twice a day therapy proved inadequate as a dual therapy and more studies are needed.
Obsolete Regimens	
Sequential therapy (not recommended as concomitant therapy will always be superior)	Amoxicillin (1 g) plus a PPI twice daily for **7** days, followed by clarithromycin (500 mg) and tinidazole (500 mg) or metronidazole (500 mg) plus a PPI all twice daily for a further **7** days (total 14 days)

Preferred PPI's: Esomeprazole 40 mg, rabeprazole 20 mg.

Table 4

Definitions of terms to describe outcome of therapy

Term	Definition
Successful	Excellent or good results.
Excellent results	Reliably achieve 95% or greater cure rates in adherent patients with susceptible infections
Good results	Reliably achieve 90% or greater cure rates in adherent patients with susceptible infections
Optimum duration	Days of therapy required to reliably achieve good to excellent results
Doses and frequency of administration	Those that will reliably achieve good to excellent results

Table 5

Treatment comparison of eradication rate with susceptible strains and resistant strains per protocol analysis

Susceptible strains	**eradication rate**	**days**
Triple therapy	>95%	14
Sequential therapy	>95%	14
Concomitant therapy	>95%	14
Bismuth quadruple therapy	>95%	14
Levofloxacin triple therapy	>95%	14
Vonoprazan triple	>95%	7
Resistant strains		
Clarithromycin triple therapy	<20%	7
Clarithromycin triple therapy	<50%	7
Sequential therapy (dual)	<20%	10
Sequential therapy (dual)	<20%	14
Hybrid therapy (dual)	<20%	14
Fluoroquinolone triple	<50%	14
Vonoprazan Triple	~80%	7