New concepts of resistance in the treatment of *Helicobacter pylori* infections

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SUMMARY

The prevalence of antimicrobial drug resistance is now so high that all patients infected with *Helicobacter pylori* should be considered as having resistant infections. Ideally, therapy should be based on pretreatment antibiotic-susceptibility testing but this strategy is not currently practical. At present, clarithromycin-containing triple therapies do not reliably produce a ≥80% cure rate on an intention-to-treat basis and are, therefore, no longer acceptable as empiric therapy. In this Review, we discuss concepts of resistance that have become part of mainstream thinking for other infectious diseases but have not yet become so with regard to *H. pylori*. We also put data on the pharmacokinetics and pharmacodynamics of the drugs used in *H. pylori* therapy and the effect of host cytochrome P450 genotypes in context with treatment outcomes. Our primary focus is to address the problem of *H. pylori* resistance from a novel perspective, which also attempts to anticipate the direction that research will need to take to provide clinicians with reliable approaches to this serious infection. We also discuss current therapies that provide acceptable cure rates when used empirically (i.e. sequential therapy; four-drug, three-antibiotic, non-bismuth-containing 'concomitant' therapy; and bismuth-containing quadruple therapy) and how they might be further improved.

KEYWORDS antibiotics, cytochrome P450, *Helicobacter pylori*, phenotypic drug resistance, therapy

REVIEW CRITERIA

PubMed was searched for papers published up to 30 November 2007 using the following terms in combination: "*H. pylori*", "resistance", "therapy", "eradication", "second", "triple", "quadruple", "sequential", and "rescue". We also reviewed the literature from the previous 10 years on the pharmacokinetics and pharmacodynamics of the drugs used in *H. pylori* therapy and the relationship of host cytochrome P450 genotype to treatment outcome. We did not perform meta-analyses. We reviewed only articles published in English. The reference list was updated in February 2008.

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INTRODUCTION

Helicobacter pylori infections are unusual, for bacterial infections, in that they typically are not considered as being in the infectious diseases area of medicine but instead are considered under gastroenterology. The usual cure rates of therapy for *H. pylori* infection are also lower than are considered acceptable for other serious, treatable, bacterial infections. For most bacterial infectious diseases appropriate therapy is devised on the basis of antibiotic-susceptibility testing, and the expectation is that more than 95% of infections—typically more than 99%—can be reliably cured with the first course of therapy. Clinicians are also generally kept up to date with regard to the drug-resistance patterns of most pathogens circulating in their community, which allows them to plan initial therapy accordingly. In addition, bacterial cultures are typically generated and therapy further adjusted according to these results. By contrast, clinicians are usually unaware of the prevalence of drug resistance among *H. pylori* isolates in their region and, although they expect high cure rates, they typically have no inkling that poor results are common.

The molecular mechanisms underlying bacterial resistance to commonly used antibiotics are well understood[1] and there have been several excellent papers that deal with the procedural or mechanical aspects of treatment (i.e. how to get around the problem of resistance).[2] In this Review, we discuss concepts of resistance that have become part of mainstream thinking for other infectious diseases but have not yet become so with regard to *H. pylori*. Some of the terms used, such as 'phenotypic antibiotic resistance', 'persister cells' and 'dormancy', may initially seem strange.[3–5] We also put data on the pharmacokinetics and pharmacodynamics of the drugs used in *H. pylori* therapy and the effect of host cytochrome P450 genotypes in context with treatment outcome. Our primary focus is to address the problem of *H. pylori* resistance from a novel perspective, which also attempts

to anticipate the direction that research will need to take to provide clinicians with reliable approaches to this serious infection.

Why *H. pylori* should be treated like other infectious diseases

Clinically, *H. pylori* infection has many similarities to syphilis or tuberculosis rather than most common acute infectious diseases. All three typically produce latent infections, and only a modest proportion of patients experience clinical manifestations.[6] *H. pylori* is silently destructive; infection leads to continuing damage to gastric structure and function and, like tuberculosis, has proved difficult to cure, generally requiring multidrug therapy. Overall, the proportion of patients who suffer clinical sequelae of *H. pylori* infection is higher than for patients with either syphilis or tuberculosis.[6,7] Although the proportion of such patients and the type of outcome vary greatly among populations, approximately 20% of individuals infected with *H. pylori* will experience clinical sequelae, generally a peptic ulcer or gastric cancer.[7]

A HISTORY OF TREATMENT FOR *H. PYLORI* INFECTIONS

For most infectious diseases, the initial approach to treatment is to identify a strategy that results in cure of all or almost all infections. Only then are attempts made to simplify the therapy—crucially, without incurring a reduction in the cure rate. Clinicians can predict treatment success from cumulative experience and from the results of antimicrobial drug susceptibility testing of isolates of the infectious agent from their patients. Cure is confirmed clinically, often by specific post-treatment tests (e.g. repeat chest X-ray after treatment for pneumonia). The development of resistance to therapy in the community is quickly recognized and results in rapid changes in practice to maintain excellent results.

Therapies for *H. pylori* infection were largely derived by using a 'hit or miss' process. Nonetheless, the goal was to develop therapies with cure rates as high as those expected for other infectious diseases.[8,9] Early approved therapies such as dual therapy with a PPI plus amoxicillin or a PPI plus clarithromycin were quickly abandoned if they failed to provide consistent cure rates of 85% or greater. By contrast, triple therapies consisting of an antisecretory drug plus amoxicillin and clarithromycin, amoxicillin and metronidazole, or clarithromycin and metronidazole were embraced as they seemed to provide consistent cure rates of at least 90%.

The first therapy to reliably provide a cure rate of >90% consisted of a bismuth salt, metronidazole and tetracycline without the addition of an antisecretory drug.[10] Subsequent experience showed that the cure rate for this treatment was reduced in the presence of metronidazole-resistant *H. pylori*, but this reduced efficacy could be largely overcome by increasing the dose of metronidazole or the duration of treatment and/or by adding a PPI.[11–13]

Although reviews and consensus statements published in the past 10 years still recommend therapy with a PPI plus amoxicillin and clarithromycin or metronidazole, they now include the caveat that such traditional triple therapy should only be used if the local prevalence of resistance is below an arbitrary level. This caveat is an indirect acknowledgment of the fact that, in almost every country for which there are data available, the actual cure rates for this triple therapy are 50–79%;[14,15] it fails to achieve the expected 90% or greater eradication rate.[14–17]

Therapy for *H. pylori* infection lost its way in part because as cure rates declined (largely because of an increasing prevalence of resistant organisms), regulatory agencies (e.g. the US FDA) did not require consistent, high cure rates for approval of new therapies. For example, instead of clearly separating clinical trial results according to the susceptibility and resistance of the *H. pylori* strain, the results were typically presented as the outcome for all patients treated. The fall in overall cure rates caused by the increasing proportion of cases with resistant infections did not result in an outcry over the need for more-effective regimens. There was also no upward adjustment of the cure rate required for new therapies to be approved or for a treatment regimen to remain FDA approved. Pharmaceutical companies were, therefore, free to do studies and to market therapies on the basis of their perceived convenience (e.g. 7 days versus 14 days) instead of on the basis of their success in terms of maintaining high cure rates. Few clinicians would recommend a therapy for latent syphilis that has a 70% cure rate, and yet the results of comparative studies of different therapies for *H. pylori* infection that have produced very low cure rates continue to be described as equivalent to one another and as acceptable therapy, rather than being described as producing unacceptably low cure rates.[18–20]

The initial studies with triple therapy achieved excellent cure rates, in part because they were done before resistance became a problem and primarily involved patients who had duodenal ulcers, which have the highest cure rates. Strong marketing messages from pharmaceutical companies assisted by physician spokespersons overshadowed the steady erosion of cure rates related to reduced durations of therapy and to an increasing proportion of resistant organisms. Routine post-treatment tests could have provided an early warning about the drop in cure rates but the general lack of easily available, accurate, noninvasive testing methods (e.g. urea breath testing or stool antigen testing) made routine testing the exception when it should have been the rule, and allowed physicians to remain swayed by consensus statements instead of their own experience.

As the worldwide cure rates with a PPI plus amoxicillin and clarithromycin have fallen into the unacceptable range (Figure 1),[14,21] unless susceptibility data are available, physicians should now assume that patients are infected with resistant strains and act accordingly.

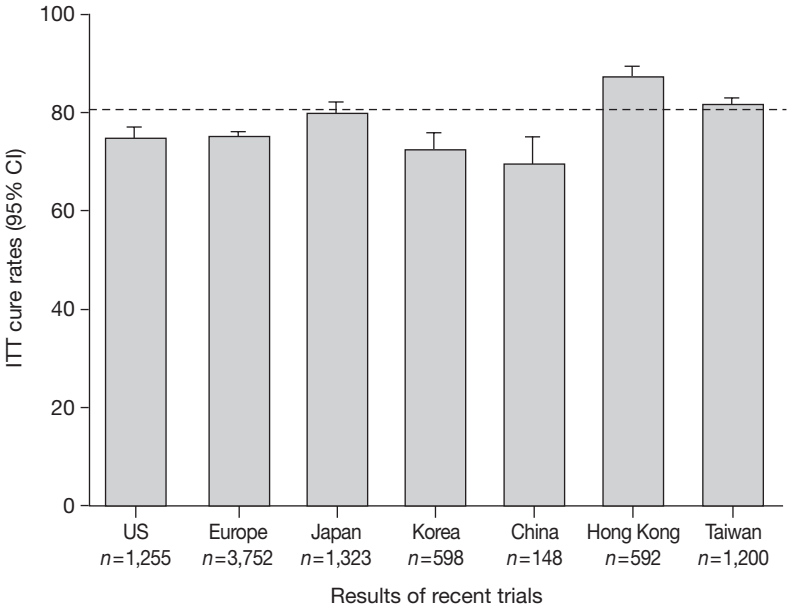

Figure 1 Results of comparison studies that included more than 100 patients and tested the combination of a PPI plus amoxicillin and clarithromycin. The dashed line signifies the threshold of an 80% cure rate. The results are shown as mean cure rates with bars denoting the 95% confidence intervals. Abbreviations: ITT, intention to treat; *n*, number of patients. Permission obtained from Blackwell © Graham DY *et al*. (2007) A report card to grade *Helicobacter pylori* therapy. *Helicobacter* **12:** 275–278.

APPROACHING *H. PYLORI* AS AN INFECTIOUS DISEASE

H. pylori infections should be approached in the same way as other serious transmissible infectious diseases, which require a commitment on the part of the physician to monitor the patient and confirm that the infection is cured.[22] Issues to be considered when selecting a regimen for treatment of an infectious disease include effectiveness, simplicity, tolerability, adverse effects, the prevalence of antibiotic resistance in the community, dose, duration, costs, and whether and how much control of gastric pH is needed. Many of these issues are discussed below in relation to the treatment of *H. pylori* infections.

Antimicrobial drug resistance

Antimicrobial drug resistance is a major cause of treatment failure and is largely responsible for the decline in eradication rates. As mentioned previously, the molecular mechanisms underlying resistance to commonly used antibiotics are well established and are not discussed further here.[1] Traditional drug-susceptibility testing is the gold standard for identifying susceptible and resistant strains. Agar dilution is the test of choice. The Epsilometer test (Etest®, AB Biodisk Ltd, Sweden) has proven clinically reliable except in the case of metronidazole, for which it tends to overestimate the presence of resistance, so Etest® results for metronidazole must, therefore, be confirmed by agar-dilution methods.[23] Molecular methods that detect specific changes in the *H. pylori* genome are alternative approaches to drug-resistance testing that can allow more rapid detection of resistance than is possible with traditional susceptibility tests, as well as allowing the use of stool or biopsy specimens to detect resistance.[24,25]

Clinically, resistance to a drug effectively removes that particular drug from the treatment equation (e.g. it turns a dual therapy into a monotherapy, a triple therapy into a dual therapy). One exception to this rule is for metronidazole and tinidazole, prodrugs that are activated in the bacterial cell by bacterial enzymes. There are several *H. pylori* nitroreductase enzymes that can potentially activate these drugs, such that increasing the dose of the drug might allow resistance to be partially overcome. In general, and in most countries, metronidazole resistance should be considered as ubiquitous and increased doses be used routinely unless it

has been proven that high cure rates are maintained with the standard doses and/or treatment durations shorter than 14 days.

Host factors that influence treatment success

Since *H. pylori* infections are typically acquired in childhood, there is no rush to start treatment. The drug regimen should be selected on the basis of susceptibility testing, using biopsies from the patient, stool specimens, or, more commonly, by knowledge of the success rates of different therapies in the local area and in a physician's practice. Other considerations include drug costs and availability, and should take into account the differences in pharmacokinetics and pharmacodynamics between the available drugs.[26–30]

Genotypic differences also have an important role in determining therapeutic success.[31] Cytochrome P450 (CYP) 2C19 (CYP2C19) is an enzyme that metabolizes PPIs such as omeprazole, lansoprazole and rabeprazole. Differences in PPI metabolism caused by polymorphisms in the *CYP2C19* gene have provided critical insights into how to improve the efficacy of therapy.[32–34]

There are three different *CYP2C19* genotypes: rapid metabolizer ($CYP2C19^{*1/*1}$), intermediate metabolizer ($CYP2C19^{*1/*X}$) and poor metabolizer ($CYP2C19^{*X/*X}$), where *1 and *X represent the wild-type and mutant alleles, respectively.[32–34] Plasma PPI levels and intragastric pH during PPI treatment are lowest in the rapid-metabolizer group, intermediate in the intermediate-metabolizer group, and highest in the poor-metabolizer group.[32–34] Eradication rates associated with triple therapy are inversely related to ability to metabolize PPIs (i.e. the rapid-metabolizer group has a lower eradication rate than the other groups).[31,34–39]

As might be expected, the *CYP2C19* genotypic differences in the pharmacokinetics and pharmacodynamics of PPI metabolism are reflected in factors such as the rate of healing of erosive esophagitis and eradication rates for *H. pylori* infection when PPI-containing regimens are used.[31] Most studies of the effects of *CYP2C19* genotypic differences have come from Asia where poor-metabolizer genotypes are relatively common. The prevalence of poor-metabolizer genotypes is low in Western populations, and some reports have suggested that the *CYP2C19* genotype may not be important in such populations.[40,41] However, others have confirmed the occurrence of improved eradication rates in poor metabolizers.[42]

Overall, when eradication rates achieved with amoxicillin-containing therapies are considered in terms of the pharmacokinetics and pharmacodynamics of the PPI being used, the results consistently show that outcome is improved when acid secretion is greatly suppressed. Physicians should, however, recognize that the patient's *CYP2C19* genotype is a surrogate marker for the degree and duration of acid secretion, such that if attention is paid to the pharmacokinetics and pharmacodynamics of the PPI chosen, the *CYP2C19* genotype can be ignored. Consequently, by choosing the correct dose and dosing interval for the PPI in question the same eradication results can be achieved in rapid metabolizers as would be seen in poor metabolizers.

Most clinical data on the enhancement of therapeutic effectiveness come from studies of dual therapy consisting of a PPI and amoxicillin. Early studies showed that the dose (e.g. approximately 2 g of amoxicillin) and duration (14 days) of therapy were important for providing good cure rates.[43] Studies in Japan in the past 8 years have shown that consistent control of intragastric pH can reliably produce cure rates of greater than 90% for this dual therapy (see below).[35–39,44–46] Importantly, however, smoking has a significant detrimental effect on the outcome of dual therapy and probably also on any therapy that contains amoxicillin.[38,44,47] This effect of smoking is probably related to its influence on acid secretion, but this association has not been well studied and needs further evaluation.

CYP3A4 and *IL1B* (the gene encoding interleukin 1β) polymorphisms also have an effect on *H. pylori* eradication rates.[48,49] Moreover, absorption of orally dosed drugs is often influenced by an ATP-dependent efflux transporter called P-glycoprotein, which is encoded by the multidrug-resistance transporter gene 1 (*MDR1*). PPIs are substrates of P-glycoprotein and there have been published reports that *MDR1* polymorphisms as well as the *CYP2C19* genotype of patients with clarithromycin-resistant *H. pylori* are significantly associated with successful eradication.[45,50]

WHY IS *H. PYLORI* DIFFICULT TO ERADICATE?

H. pylori infections present many challenges when it comes to effective antimicrobial therapy,

some of which are unique to *H. pylori* and others that are common to many infections. The unique challenges relate to the fact that *H. pylori* bacteria in the stomach are protected from the acidic environment by a thick mucus layer. In addition, as the stomach constantly secretes acid and periodically empties its contents, topical therapy tends to be diluted and washed out.[8] The effectiveness of many antimicrobial drugs is greatly diminished at acidic pHs, which makes control of pH critical for them to be effective. It is not by chance that the first truly effective therapy for *H. pylori* infection was a combination of three relatively pH-insensitive antimicrobial drugs (bismuth, tetracycline and metronidazole).[10]

The number of *H. pylori* organisms in the stomach is very large, and this high bacterial burden produces an inoculum effect (see below). A proportion of *H. pylori* bacteria are attached to gastric mucosal cells and form a biofilm, and some are intracellular, which means they are inaccessible to many antibiotics. These three phenomena are largely responsible for the relative resistance of *H. pylori* to antimicrobial therapy and insights can be gained into ways to overcome these features by examining advances made for other infections. Tuberculosis is a potentially good source of information as both it and *H. pylori* infection require treatment with multiple drugs for a long duration.[3] Tuberculosis typically is associated with a high bacterial burden. High bacterial loads make it likely that antibiotic-resistant strains will be present when antibiotic therapy is begun. The small number of genetically resistant stains present at this stage can be overcome by the use of multiple drugs, which reduce the chance that a resistant strain will survive.

Infections associated with a high bacterial burden are also characteristically ones in which phenotypic (reversible) antibiotic resistance is also present. Phenotypic resistance (our preferred term) often results from the presence of a population of nonreplicating (i.e. dormant) bacteria—the persister population—that can survive until antibiotic therapy is stopped.[3–5] Clinically, phenotypic resistance is characterized by treatment failure without the development of resistance, which allows the patient to be treated with the same antibiotic combination again. Phenotypic resistance is a feature of dual therapy with a PPI plus amoxicillin, but is also seen with other therapies. Treatment failure without the development of resistance has, on occasion, been characterized as a positive attribute of some therapies, compared with treatment failure associated with the development of resistance.

As suggested above, the presence of phenotypic resistance indicates that the duration of therapy was insufficient. For this reason, extended-duration therapy may eradicate persister populations of bacteria as they oscillate between nonreplicating and replicating states or between intracellular and extracellular environments (i.e. from phenotypically resistant to phenotypically susceptible states). Clinically, if the factors responsible for phenotypic resistance could be overcome, bacteria could be prompted to re-enter the replicative state and thus become susceptible to antibiotics. This concept is not new, as it was first described by Bigger in 1944.[51] As *H. pylori* does not replicate at a pH below 6, it has been suggested that a pH lower than 6 in the microenvironment surrounding *H. pylori* is responsible for maintaining the bacteria in a nonreplicative state, which means that increasing the local pH might restore replication.[52] This concept has provided the theoretical basis for the successful revival of dual therapy with a PPI plus amoxicillin (see below).[46]

PREDICTING THE EFFECT OF RESISTANCE ON TREATMENT SUCCESS

The results of different combinations of dual therapy (such as a PPI plus amoxicillin, PPI plus clarithromycin, or PPI plus metronidazole) were established long ago, as were the differences that can be expected by changing the dose and duration of these treatment combinations.[13,53–57] Generally, the results of such therapy in the face of specific antimicrobial drug resistance mirror what would be expected if that antibiotic were removed from the combination. For example, in the face of clarithromycin resistance, triple therapy with a PPI plus amoxicillin and clarithromycin effectively becomes dual therapy with a PPI plus amoxicillin: likewise, triple therapy with a PPI plus metronidazole and clarithromycin becomes dual therapy with a PPI plus metronidazole. As noted above, the success of the PPI plus amoxicillin combination is greatly influenced by treatment duration, such that, in the presence of clarithromycin resistance, a cure rate of approximately 25% is expected after 1 week of therapy, which increases to 50% with 2 weeks of therapy.[43,53] Amoxicillin resistance

Table 1 A report card for scoring the outcome of therapy for *H. pylori* infection on an intention-to-treat basis.

Grade	Intention-to-treat cure rate (%)	Score
A	≥95	Excellent
B	90–94	Good
C	85–89	Acceptable
D	81–84	Poor
F	≤80	Unacceptable

Permission obtained from Blackwell © Graham DY *et al.* (2007) A report card to grade *Helicobacter pylori* therapy. *Helicobacter* **12:** 275–278.

Box 1 The authors' therapeutic recommendations in an era of increased clarithromycin and metronidazole resistance.[a]

Bismuth-containing quadruple therapy
- A bismuth salt and tetracycline hydrochloride 500 mg four times daily
- A bismuth salt and tetracycline hydrochloride 500 mg three times daily, plus metronidazole or tinidazole 500 mg three times daily, plus a PPI twice daily

Sequential therapy[b,c]
- A PPI plus amoxicillin 1 g twice daily for 5 days followed by the PPI plus clarithromycin 500 mg and tinidazole or metronidazole 500 mg twice daily for 5 days

Concomitant therapy[c,d]
- A PPI plus amoxicillin 1 g, clarithromycin 500 mg and tinidazole or metronidazole 500 mg twice daily for 7–14 days

High-dose dual therapy[e]
- High-dose PPI plus amoxicillin 500 mg every 6 h for 14 days

[a]See text for details. [b]The eradication rate achieved with sequential therapy could probably be improved to a Grade A result by increasing the treatment duration and/or continuing amoxicillin throughout the entire treatment period. [c]Triple-therapy dose packs can be used for concomitant therapy by adding tinidazole or metronidazole twice daily. Neither sequential nor concomitant therapy is recommended as a salvage therapy. [d]Concomitant therapy consists of four drugs, three of which are antibiotics. We recommend treatment for 14 days; this recommendation is based on the concept that 'longer is better' in terms of treatment duration, but this regimen remains to be adequately tested. [e]This approach has been shown to be very effective in Japan and in some European studies, but studies are needed to identify the best PPI and PPI doses for use in Western populations.[35–39,46] High-dose implies that the effectiveness of PPI-based acid suppression is equivalent in patients with *CYP2C19* rapid-metabolizer and poor-metabolizer genotypes.

and tetracycline resistance are both rare, and bismuth resistance does not occur, which means that these three drugs can generally be used in any situation.

RECOMMENDATIONS FOR INITIAL TREATMENT

H. pylori infections are bacterial infections and there is a tremendous amount of literature and history on the treatment and the expectations of treatment with antibiotics. To aid assessment of the results of antibiotic therapy and comparison of therapeutic regimens in an objective manner, we have developed a scoring system based on effectiveness categories.[14] The scoring system for treatment results uses a report card with grades A, B, C, D, and F, which is similar to that used to grade the performance of school children (Table 1). The category of A or 'excellent' is based on the cure rates of therapy expected for essentially all bacterial infectious diseases other than *H. pylori* (i.e. ≥95% on an intention-to-treat [ITT] basis).

As noted above, triple therapies that use combinations of a PPI plus amoxicillin, clarithromycin, metronidazole or tinidazole provide unacceptably low eradication rates in most regions of the world (Grade F, ≤80% ITT cure rate) and unless there are data that confirm a particular triple therapy is still effective in a particular region, it should not be prescribed as empiric therapy.[14] In our opinion there are at least four treatment options available that are effective in most areas (Box 1): traditional quadruple therapy, sequential therapy, 'concomitant therapy' (non-bismuth-containing therapy with four drugs, three of which are antibiotics), and dual therapy (including special therapies based on dual therapy). A Grade A result (≥95% ITT eradication rate) should always be striven for, but we may need to accept a Grade B result (90–94% ITT success rate) (Figure 1).[14] In addition, and importantly, physicians should routinely accept responsibility for ensuring that eradication of *H. pylori* has been successful in their patients (see below).

Quadruple therapy

Traditional quadruple therapy consists of a bismuth salt, tetracycline hydrochloride, metronidazole or tinidazole, and a PPI given three or four times daily. In most countries more than 10% of patients will be infected with metronidazole-resistant *H. pylori*, and so the dose of metronidazole should be approximately 1,500 mg and

the duration of treatment should be 14 days. However, this quadruple therapy can only be used in countries where bismuth is available.

Sequential therapy

Sequential therapy was originally described as a 10-day therapy, in which the first 5 days consisted of dual therapy with a PPI and amoxicillin given twice daily, followed by triple therapy consisting of a PPI, clarithromycin, and tinidazole or metronidazole twice daily to complete the 10 days. Sequential therapy typically produces Grade B results and is proven to be superior to traditional triple therapy, which produces a Grade F result.[58] The results of sequential therapy could perhaps be improved to Grade A level by continuing the amoxicillin throughout the entire treatment period and/or by extending the treatment duration to 14 days, but studies are need to test these hypotheses. Sequential therapy is not a good choice in the presence of resistance to both clarithromycin and metronidazole and is, therefore, not an acceptable choice for treatment after multiple failed therapies.[59]

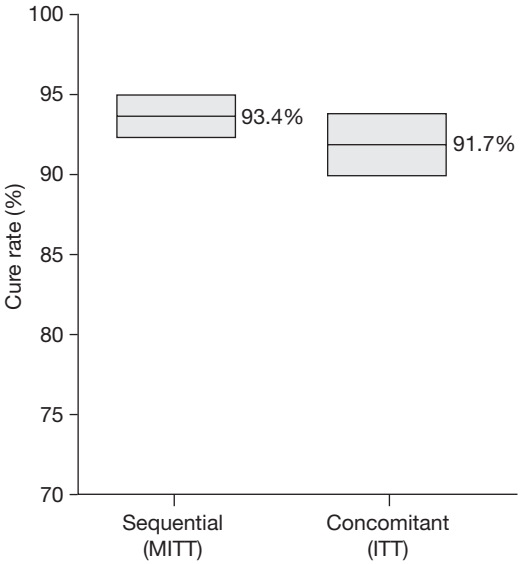

Figure 2 Weighted means and 95% confidence intervals for *H. pylori* eradication rates in 16 studies of sequential therapy ($n = 1,805$) for 10 days[58] and 9 studies of concomitant therapy ($n = 715$) for 3–7 days.[60–68] Abbreviations: ITT, intention to treat; MITT, modified intention to treat.

Concomitant therapy

Concomitant therapy—non-bismuth-containing, four-drug, three-antibiotic therapy—was introduced before sequential therapy and there is experience of its use in about 1,000 patients.[60–68] It consists of four drugs—a PPI, clarithromycin, metronidazole or tinidazole, and amoxicillin—all given twice daily. The duration of concomitant therapy has ranged from 3 days to 7 days and it has produced Grade B results, similar to those obtained with sequential therapy[60–68] (Figure 2). Studies are needed to test whether extending the duration of therapy will improve these results.

As with sequential therapy, concomitant therapy would probably be a poor choice in the presence of *H. pylori* that are resistant to clarithromycin and metronidazole, or for treatment after multiple drug regimes have failed, as those patients can be expected to have multidrug-resistant infections. Importantly, however, traditional triple therapy can easily be converted to concomitant therapy by the addition of 500 mg of metronidazole or tinidazole twice daily.

Dual therapy and dual-therapy-based special therapies

Dual therapy with a PPI plus amoxicillin has been revived on the basis of results obtained after considering the issues in terms of pharmacokinetics and pharmacodynamics. As noted above, the good results of this therapy in patients with *CYP2C19* poor-metabolizer genotypes suggest that if sufficient PPI is provided to achieve the same acid-suppressive effect in rapid metabolizers as it has in poor metabolizers (i.e. irrespective of the *CYP2C19* genotype), dual therapy should be a successful approach and reliably provide Grade A or Grade B results. Studies are needed in Western populations to confirm the success seen in Japan and to identify the dose and dose intervals needed for each PPI to ensure the best results are achieved. Clinical trials in Japan have suggested that approximately 80 mg of omeprazole given every 12 h is sufficient.[36] Clinical studies with PPI dosing every 6 h have also proven successful in Japan.[46,69] We hope that comparative studies of PPIs administered every 6, 8, or 12 h with approximately 2 g of amoxicillin for 14 days will be performed to improve the accuracy of estimates of what eradication rates can be obtained with different PPIs. Smokers should probably be studied separately or at least identified as smokers because, as mentioned earlier, smoking has a detrimental effect on the outcome of dual therapy. Ideally, dual therapy should use a sufficient PPI dose to overcome any detrimental effects of smoking.

Amoxicillin plus PPI dual therapy could also provide the basis for the addition of a third or fourth drug, given either as a sequential therapy or as a concomitant therapy. The dual-therapy (PPI plus amoxicillin) component at standard doses for 2 weeks is expected to provide a cure rate of approximately 50%; the addition of a third, or third and fourth drug(s) would then bring the cure rate up to acceptable levels. Higher and more frequent PPI dosing than standard would be expected to raise the basal cure rate and thus the overall success rate, even if success related to the additional components remained unchanged. Studies are also needed to test whether this increased success actually occurs.

Fluoroquinolones, furazolidone, rifabutin and other possibilities

The four treatment options outlined above all have the potential to be modified with new or alternative drugs. Generally, new drug combinations are concocted from existing regimens by substituting a new drug for one that is subject to increasing resistance. For triple therapy, therefore, the new drug is generally substituted for clarithromycin and in quadruple therapy for metronidazole. The concept is based on the premise that successful treatment requires drugs that have not been used before.

Treatment with fluoroquinolones such as levofloxacin and moxifloxacin is currently in vogue, generally in the form of a PPI plus amoxicillin plus fluoroquinolone combination.[42,62] The best initial approach to identification of a good new therapy or to elimination of a bad one is to use a high dose of the drugs being tested and a long treatment duration. Only if the results are good can studies to simplify the treatment be planned, but it is critical that such regimes maintain treatment effectiveness. This approach has rarely been implemented. As meta-analyses have shown, short-duration fluoroquinolone results (e.g. 7 days) were significantly inferior (e.g. Grade F) to treatment for 10 days, which itself only produced a Grade C result (85–89% ITT cure rate).[70] Unfortunately, fluoroquinolone resistance has been rapidly increasing and these drugs will probably be rendered useless before an effective protocol is devised. Clearly, fluoroquinolones should not be given to patients who have received fluoroquinolones in the past, as resistance is essentially assured.

Rifabutin and furazolidone are especially useful for patients who have experienced multiple treatment failures because these antibiotics are rarely used and, therefore, resistance to them is unlikely. Like bismuth, furazolidone is not available in many countries: it is no longer sold in the US as the company that marketed it was bought out and the market was small; furazolidone is, however, still available in Mexico. We substitute furazolidone for metronidazole in quadruple therapy.

THINKING OUTSIDE THE BOX: THE USE OF TREATMENT ENHANCERS

There is considerable interest in the use of probiotic bacteria to enhance the effectiveness of antimicrobial therapy for *H. pylori*. Two recent meta-analyses suggest that probiotics are associated with modest increases in eradication rates and reductions in adverse effects.[71,72] Studies are needed to identify which probiotic strains to use and what is the best delivery system to achieve reliable results. Probiotics are not inexpensive, and so cost will need to be taken into consideration, especially if their benefits are minor.

Pronase and N-acetyl cysteine have been used to reduce the gastric mucus layer, which could potentially expose *H. pylori* bacteria. In one trial, 18,000 tyrosine units of pronase given three times daily for 14 days significantly increased the effectiveness of traditional triple therapy (the cure rate increased from 76.5% to 94%, $P<0.05$).[73] Clearly, additional studies are needed to examine nonantibiotic treatment enhancers.

CONCLUSIONS

H. pylori cause a serious, transmissible, infectious disease. The increasing prevalence of drug resistance has complicated successful therapy, such that what is and is not appropriate therapy must be reconsidered. Advances have shown that phenotypic and genetic resistance to therapy can be successfully dealt with, and what still needs to be done is now clearly identifiable. Ideally, therapy should be based on pretreatment drug-susceptibility testing, and empiric use of eradication therapies should assume the presence of antimicrobial drug resistance and use increased doses for 14 days. Clarithromycin-containing triple therapies now typically produce ≤80% ITT cure rates (Grade F) and are thus no longer acceptable as empiric therapy. Current options for initial treatment include sequential therapy, concomitant therapy, and bismuth-containing quadruple therapy. An improved appreciation of the role of gastric pH in phenotypic resistance

has resulted in high cure rates with high-dose PPI plus amoxicillin dual therapy, although studies are still needed to devise improved dual-therapy-based multidrug regimes. Selection of appropriate antimicrobial drugs following treatment failure is best approached by drug-susceptibility testing. If such testing is not available, we recommended a bismuth-containing quadruple therapy, with substitution of a new drug for the metronidazole or tinidazole and/or the clarithromycin if these agents have been used previously. One alternative approach would be to use 14 days of treatment with a high-dose PPI and amoxicillin-containing triple therapy with rifabutin, a fluoroquinolone, or furazolidone.

KEY POINTS

- Traditional triple therapy remains effective only when used to treat infections with susceptible organisms
- The prevalence of antibiotic resistance has increased to such an extent that, to maintain acceptable cure rates, all patients should be considered as having resistant infections
- Therapies that do not reliably yield ≥90% cure rates on an intention-to-treat basis should not be prescribed empirically; triple therapies that contain combinations of a PPI, amoxicillin, clarithromycin or metronidazole now typically yield cure rates <80% and are no longer acceptable as empiric therapy
- Initial empiric therapy options currently include the following: sequential therapy; concomitant, four-drug, antibiotic therapy; and bismuth-containing, high-dose metronidazole, quadruple therapy
- Sequential and concomitant (i.e. four drugs, three of which are antibiotics) therapies have the potential to be improved by simple measures such as increasing the duration of treatment
- High-dose, frequent-administration PPI therapy can reduce phenotypic resistance and should increase the cure rates achieved with amoxicillin-containing dual therapy into the acceptable range

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