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Newer concepts regarding resistance in the treatment

Helicobacter pylori infections

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Summary

The prevalence of antimicrobial resistance is now such that all patients should be considered as having resistant infections. Ideally therapy is based on pretreatment susceptibility testing. Empiric therapies should assume antimicrobial resistance and use higher doses for 14 days. Acceptable results are 90–94% cure intention to treat (Grade B) or greater. Clarithromycin-containing triple therapies now typically produce $\leq 80\%$ cure ITT (Grade F) and are no longer acceptable empiric therapy. Current initial therapy options are between sequential therapy, concomitant therapy, and bismuth containing quadruple therapy. Sequential therapy has the potential to be improved to $\geq 95\%$ cure ITT (Grade A) by continuing the amoxicillin through the second and/or by increasing the duration. Better appreciation of the role of acidity in phenotypic resistance has resulted in high cure rates with high dose PPI plus amoxicillin dual therapy; additional studies to devise better dual-based multidrug regimes are still needed. Antimicrobial choices following treatment failure is best approached by susceptibility testing. If not available, we recommended a bismuth containing quadruple therapy substituting a new drug for metronidazole/tinidazole and/or clarithromycin if they have been used previously. The alternate would be to use a 14 day high dose PPI, amoxicillin-based triple therapy with rifabutin, a fluoroquinolone, or furazolidone.

Keywords

Helicobacter pylori; therapy; resistance; antibiotics; anti-secretory drugs; phenotypic drug resistance; cytochrome P450

“To read without reflecting is like eating without digesting”.

Edmund Burke

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Review criteria: We searched the relevant papers by using computer-assisted bibliographic searches of PubMed through November 30, 2007 using combinations of the following terms: *H. pylori* combined with resistance, therapy, eradication, second, triple, quadruple, sequential, or rescue. We also reviewed the recent literature on pharmacokinetics and pharmacodynamics in relation to the drugs used in *H. pylori* therapy and the relation to host cytochrome P450 genotypes to treatment outcome. We did not perform meta-analyses. We reviewed only articles published in English.

Introduction

H. pylori infections are unusual for bacterial infections in that they typically are considered as not being in the “Infectious Diseases” part of the book and instead are considered under “Gastroenterology”. The usual cure rates of therapy are also less than considered acceptable for other serious treatable bacterial infections. With most bacterial infectious diseases an appropriate therapy is devised based on antimicrobial susceptibility testing and clinicians expect to be able to reliably cure more than 95%, typically more than 99% of infections with the first course of therapy. Clinicians are also generally kept up to data regarding the resistance patterns of most pathogens circulating in their community which allows them to plan their initial therapy accordingly. In addition, cultures are typically done and the therapy can be further adjusted according to those results. In contrast, clinicians are usually ignorant of the prevalence of resistance among *H. pylori* in their region and while they expect high cure rates typically have no inkling that poor results are common.

The molecular mechanisms of resistance to commonly used antibiotics are well understood¹ and there have been a number of excellent recent papers dealing with the procedural or mechanical aspects of treatment (ie, how to get around the problem of resistance) (eg, reference²). One goal of this paper is to introduce concepts of resistance that have become part of the mainstream thinking for other infectious diseases but have not yet become main stream with regard to *H. pylori*. Some of the terms may initially appear strange to clinicians such as phenotypic antibiotic resistance, persister cells, and dormancy³⁻⁵. In addition, we attempt to put data dealing with the pharmacokinetics and pharmacodynamics of the drugs used in *H. pylori* therapy as well the effect of host cytochrome P450 genotypes in relation to treatment outcome. Our primary focus has been to address the problem from a different prospective which attempts to also anticipate the direction research will take in providing clinicians reliable approaches to this serious infection.

Clinically, *H. pylori* infections have many similarities to syphilis or tuberculosis rather than most common acute infectious diseases. All three are typically latent with only a modest proportion of patients experiencing clinical manifestations⁶. *H. pylori* is silently destructive leading to continuing damage to gastric structure and function and like tuberculosis, it proved difficult to cure, generally requiring multidrug therapy. Overall, the proportion of patients who suffer clinical outcomes of *H. pylori* is higher than with either syphilis or tuberculosis. Although the proportion and the type of outcomes varies greatly among populations, overall, approximately 20% of infected will experience a clinical outcome, typically a peptic ulcer or gastric cancer⁷.

History of treatment of *H. pylori* infections differs from other infectious diseases

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

H. pylori therapies were largely derived by the process of “hit or miss”. Nonetheless, the goal was to develop therapies with cure rates as high as expected for other infectious diseases^{8, 9}. For example, early approved therapies such as dual therapy with a proton pump inhibitor (PPI) and amoxicillin or a PPI plus clarithromycin were quickly abandoned because they failed to

consistently provide cure rates of 85% or greater and triple therapies consisting of an antisecretory drug plus amoxicillin plus clarithromycin, amoxicillin plus metronidazole, or clarithromycin plus metronidazole were embraced as they appeared to consistently provided cure rates of at least 90%.

The initial successful therapy consisted of a bismuth salt, metronidazole, and tetracycline and provided a cure rate of >95% even without the use of an antisecretory drug¹⁰. Subsequent experience showed that the cure rate was reduced in the presence of metronidazole resistant *H. pylori* and that this could be largely overcome by increasing the dose of metronidazole and duration and/or adding a PPI^{11–13}.

Although recent reviews and consensus statements appear to still recommend traditional PPI, amoxicillin, clarithromycin or metronidazole triple therapy, they include a caveat that traditional triple therapy should only be used if the resistance rate is below some arbitrary level. This is actually an indirect acknowledgment of the fact that in almost every country where there are data, the cure rates are between 50 and 79%^{14, 15} and thus fail to achieve the previously expected 90% or greater eradication rate^{14–17}.

Therapy went “off track” in part because as the success rates declined (largely because of an increasing prevalence of resistant organisms), the regulatory agencies (eg, the US Food and Drug Administration) choose not to re-level the playing field. For example, instead of clearly separating the results with regard to susceptible and resistant *H. pylori*, the results of clinical trials were typically presented as the outcome of all patients treated. Because the bar for success was relatively low the fall in overall cure rates caused by the increasing proportion of cases with resistant infections was obscured. There was also no adjustment of the cure rate required for approval even among susceptible infections. Pharmaceutical companies were therefore free to do studies and to market on the basis of perceived convenience (eg, 7 days vs. 14 days) instead of on the basis of success in terms of maintaining high cure rates. Few would consider recommending a therapy with a 70% cure rate for latent syphilis and yet comparative studies with low cure rates continue to be described as equivalent rather than as have 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 with duodenal ulcer which have the highest cure rates. Strong marketing assisted by physician spokespersons overshadowed the steady erosion of cure rates related to shorter durations of therapy and to an increasing proportion of resistant organisms. Routine post treatment testing could have provided an early warning but the general lack of easily available, accurate, non-invasive testing methods (eg, 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.

Because worldwide the cure rates with PPI, amoxicillin and clarithromycin triple therapy have fallen into the unacceptable range (Figure 1)^{14, 21}, unless one has susceptibility data, one should now assume that their patients are infected with resistant strains and act accordingly.

Approach to *H. pylori* as an infectious disease

Issues to be considered when selecting a regimen for treatment of an infectious disease include effectiveness, simplicity, tolerability, side effects, the rate of antibiotic resistance in the community, dose, duration, costs, and whether and how much control of pH is needed. Many of these are discussed below in relation to *H. pylori*. *H. pylori* infections should be approached as other serious transmissible infectious diseases which requires a commitment on the part of the physician to follow the patient and confirm that the infection is cured²².

Antimicrobial Resistance

Antimicrobial resistance is a major cause of treatment failure and is largely responsible for the reduction in eradication rates. The molecular mechanisms of resistance to the commonly used antibiotics are well established and will not be discussed further here¹. Traditional susceptibility testing is the gold standard to separate susceptible and resistance strains. Agar dilution is the recommended test of choice although the Etest has proven to provide clinically reliable except with metronidazole where it tends to overestimate the presence of resistance and must be confirmed by agar dilution methods. Molecular methods of detection of specific changes in the organisms' genome are alternative approaches to detection of resistance and in theory allow a more rapid detection of resistance as well as detection of resistance using stool or biopsy specimens^{23, 24}.

Clinically, the presence of resistance effectively takes that particular drug out of the treatment equation (ie, turns a dual therapy into a monotherapy, a triple therapy into a dual therapy as so forth). One exception is metronidazole/tinidazole which are prodrugs that are activated in the bacterial cell by bacterial enzymes. There are a number of *H. pylori* nitroreductases that can potentially activate these drugs such that increasing the dose of the drug may allow resistance to be partially overcome. In general, in most countries one should consider that metronidazole resistance is present and routinely employ higher doses unless it has been proven that high rates are maintained with lower doses.

Host factors influencing treatment success

Since the infection was typically acquired in childhood, there is no rush to start treatment. The drug regimen should be based 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 one's practice. Other considerations include cost and availability of drugs and should take into account the difference in pharmacokinetics and pharmacodynamics of the drugs available^{25–29}.

Genotypic differences also play an important role in therapeutic success³⁰. Cytochrome P450 (CYP) 2C19 is a polymorphic enzyme metabolizing proton pump inhibitors such as omeprazole, lansoprazole and rabeprazole and differences in PPI metabolism have provided critical insights into how to achieve more effective therapy^{31–33}. Genotypes of CYP2C19 are classified into three groups, rapid metabolizer (RM: *1/*1), intermediate metabolizer (IM: *1/*X) and poor metabolizer (PM: *X/*X) (*1 and *X represent the wild-type and mutant allele, respectively). Plasma PPI levels and intragastric pHs during PPI treatment in the RM group are lowest, those in the IM group come next, and those in the PM group are highest among the three groups. Eradication rates with triple therapy are inversely related to the ability to metabolize the PPIs (ie the RM group has lower eradication rate compared to other groups)^{30, 33–38}.

As might be expected, these CYP2C19 genotypic differences in pharmacokinetics and pharmacodynamics of PPIs are reflected in factors such as healing of erosive esophagitis and eradication rates for *H. pylori* infection using PPI-containing regimens³⁰. The majority of studies have come from Asia where poor metabolizers are relatively common. The frequency of poor metabolizers is low in Western populations and although some reports have suggested that CYP2C19 genotypes may not be important in Western populations^{39, 40}. However, others have confirmed the phenomena of improved results with poor metabolizers⁴¹. Overall, when one considers the results of amoxicillin containing therapies in terms of the pharmacokinetics and pharmacodynamics of the PPI, the results are consistent. It is important to recognize that the CYP2C19 genotype is a surrogate marker for the degree and duration of acid secretion such that if one pays attention to the pharmacokinetics and pharmacodynamics of the PPI chosen,

one can ignore the CYP2C19 genotype and by choosing the correct dose and dosing interval achieve the same effects in rapid metabolizers as would be seen in poor metabolizers.

The majority of clinical data regarding enhancement of effectiveness of therapy come from studies of the dual therapy consisting of a PPI and amoxicillin. Early studies showed that dose (eg, approximately 2 grams of amoxicillin) and duration (14 days) were important in providing good cure rates⁴². Recent studies in Japan have shown that consistent control of intragastric pH can reliably produce cure rates of greater than 90% for this dual therapy (see below). It is important to note that smoking has a significant detrimental effect on outcome of dual therapy and likely on any therapy containing amoxicillin^{37, 43, 44}. The effect of smoking is probably related to its effects on acid secretion but this has not been well studied and will need further evaluation.

CYP3A4 and IL1B -511 polymorphisms are also shown to have effects on eradication rates^{45, 46}. Moreover, absorption of orally dosed drugs is often influenced by an ATP-dependent efflux transporter, P-glycoprotein (P-gp). PPIs are involved in substrates of P-glycoprotein (P-gp) which is coded by *MDR1* (multi-drug resistant transporter gene 1) and it has been reported that *MDR1* polymorphism as well as *CYP2C19* genotypes of patients with clarithromycin-resistance of *H. pylori* were significantly associated with successful eradication^{47, 48}.

Why are *H. pylori* difficult to eradicate?

H. pylori infections present many challenges to effective antimicrobial therapy some of which are unique to *H. pylori* and others are experienced in the treatment of many infections. The “unique” group relate to the fact that *H. pylori* is present in the stomach where they are protected by a thick mucus layer and an acidic environment. In addition, the stomach is constantly secreting acid and emptying its contents such that typical therapy tends to be diluted and washed out⁸. The effectiveness of many antimicrobials is greatly diminished at acid pH making pH control critical for them to be effective. It is not by chance that the first truly effective therapy was a combination of three relatively pH insensitive antimicrobials (bismuth, tetracycline and metronidazole)¹⁰.

The number of *H. pylori* in the stomach is very large which produces an inoculum effect or high bacterial burden (see below). A proportion of the organisms are attached to gastric mucosal cells producing a biofilm, and finally some *H. pylori* are intracellular where they may be inaccessible to many antibiotics. These three phenomena are largely responsible for the relative resistance to effective antimicrobial therapy and one can gain insights into approaches to overcoming them by examining advances made in other infections. Tuberculosis is a potentially good source of information as both it and *H. pylori* require multiple drugs for long durations of treatment³. Tuberculosis is a typical high bacterial burden infection. High bacterial loads make it more likely that antibiotic resistant strains will be present in the population present when antibiotic therapy is begun. This low prevalence of genetic resistance can be overcome by the use of multiple drugs which reduce the chance that a resistant mutant will survive.

High bacterial burden infections are also characteristically ones where phenotypic (reversible) antibiotic resistance is also present. Phenotypic resistance is one of the terms used to describe the presence of persister populations and is related to dormancy^{3–5}. We will preferentially use the term phenotypic resistance which is characterized by treatment failure without development of resistance allowing the patient to be treated with the same antibiotic combination again. Phenotypic resistance is a feature of dual PPI plus amoxicillin therapy but is also seen with other therapies. In fact, treatment failure without developing resistance has on occasion been characterized as a positive attribute compared to treatment failure associated with the development of resistance. Phenotypic resistance often results from the presence of a population of nonreplicating (dormant) bacteria (the persister population) that survive until the

therapy is stopped. Longer term therapy may eradicate these bacteria when they oscillate between the nonreplicating and replicating state or from intracellular to extracellular environments (ie, from a phenotypically resistant to a phenotypically susceptible state) (ie, as suggested above, the presence of phenotypic resistance suggests that the duration of therapy was insufficient). Clinically if one could overcome the factors responsible for phenotypic resistance they could prompt the bacteria to reenter the replicative state and become susceptible to the antibiotics. This concept is not new as it was first described by Bigger in 1944⁴⁹. In *H. pylori* infections, it has been suggested that pH lower than 6 in the microenvironment surrounding the bacteria is responsible for maintaining the bacteria in a nonreplicative state as *H. pylori* do not replicate at pH's below 6 such that increasing the local pH may restore replication⁵⁰. This concept has been the theoretical basis for the successful revival of PPI plus amoxicillin dual therapy⁵¹ (see below).

Predicting the effect of resistance on treatment success

The results of different combinations of dual therapy such as a PPI plus amoxicillin, plus clarithromycin, plus metronidazole were established long ago as well as differences that can be expected by changes in dose and duration of these combinations^{13, 52–56}. Generally, the results of therapy in the face of specific antimicrobial resistance mirror what would be expected based on loss of the antibiotic from the combination. For example, in the face of clarithromycin resistance, the PPI plus amoxicillin plus clarithromycin effectively becomes a PPI plus amoxicillin dual therapy, or a PPI plus metronidazole plus clarithromycin becomes a PPI plus metronidazole dual therapy. As noted above the success with the PPI plus amoxicillin combination is greatly influenced by duration such that, in the presence of clarithromycin resistance, one expects a cure rate of approximately 25% after one week triple therapy increasing to 50% with 2 weeks therapy. Amoxicillin resistance is rare as is tetracycline resistance. Bismuth resistance does not occur and thus these three drugs can generally be used in any situation.

Treatment recommendations for initial treatment

H. pylori infections are bacterial infections and there is a tremendous literature and history regarding treatment and treatment expectations of therapy of antibiotic therapy. Here we use the system we proposed to assess the results of therapies. It is based effectiveness categories and is designed to allow clinicians to objectively identify and compare regimens¹⁴. We proposed scoring system of treatment results using a report card with grades A, B, C, D, and F similar to that used to grade the performance of school children (Figure 2). The category of A or “excellent” was based on what the cure rates expected essentially all other bacterial infectious diseases.

As noted above, triple therapies using combinations of PPI, amoxicillin, clarithromycin or metronidazole/tinidazole provide unacceptably low eradication rates in most regions of the world (Grade F) and unless there are data that the therapy is still effective in a particular region, it should not be prescribed as empiric therapy. In our opinion there are at least four options (Table 1). Traditional quadruple therapy, sequential therapy, concomitant (4-drugs 3-antibiotics) therapy or simply “concomitant therapy”, and dual therapy including dual therapy-based therapies. One should always strive for a Grade A result (95% or greater eradication rate, intention to treat) but may need to accept a Grade B result (90 – 94% success) (Figure 1)¹⁴. It is also important for physicians to also routinely accept responsibility for ensuring that the patient has successful *H. pylori* eradication (see below).

Quadruple therapy consists of a bismuth salt, tetracycline HCl, metronidazole/tinidazole, and a PPI given three or four times daily. In most countries one should consider that more than 10% of the patients will have metronidazole resistant *H. pylori* and thus the dose of

metronidazole should be approximately 1,500 mg and the duration should be 14 days. However, this therapy can only be used in countries where bismuth is available.

Sequential therapy was originally described as a 10 day therapy in which the first 5 days consisted of a dual therapy with a PPI and amoxicillin given b.i.d., followed by a triple therapy consisting of PPI, clarithromycin and tinidazole/metronidazole b.i.d. to complete 10 days. It typically produces Grade B results and is proven to be superior to traditional triple therapy which produces a Grade F result⁵⁷. It is probable that the results can be improved to Grade A results by continuing the amoxicillin throughout the entire treatment period and/or by extending the duration to 14 days. Studies to examine these hypotheses are needed. Sequential therapy is also not a good choice in the presence of combined clarithromycin and metronidazole resistance and therefore is not an acceptable choice for treatment after multiple failed therapies⁵⁸.

Concomitant therapy was introduced before sequential therapy and there is experience with about 1,000 patients. It consists of all four drugs (the PPI, clarithromycin, metronidazole/tinidazole, and amoxicillin being given b.i.d.). The duration has ranged from 3 to 7 days and it has resulted in Grade B results similar to those obtained with sequential therapy^{59–67} (Figure 3). As with sequential therapy, studies are needed to test whether extending the duration of therapy will improve the results.

As with sequential therapy, concomitant therapy would probably be a poor choice in the presence of dual resistant *H. pylori* or for treatment after multiple drug failures. However, it is important to note that traditional triple therapy can easily be converted to concomitant therapy by the addition of 500 mg of metronidazole/tinidazole b.i.d.

Dual therapy and dual therapy-based special therapies

Dual PPI plus amoxicillin therapy has been revived based on the results obtained after thinking about the issues in terms of pharmacokinetics and pharmacodynamics. As noted above, the results with CYP2C19 poor metabolizers suggests that if one provides sufficient PPI to achieve the same effect in rapid metabolizers as poor metabolizers (ie, 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 dosing intervals of each PPI to ensure the best effect. Clinical trials have suggested that approximately 80 mg of omeprazole given every 12 hours was sufficient³⁶. Clinical studies with every 6 hour dosing have proven successful in Japan^{51, 68}. We hope to see comparative studies of PPI being administered every 6, 8, and 12 hours with approximately 2 grams of amoxicillin for 2 weeks. Smokers should probably be randomized separately or at least identified as such as smoking is an important factor. Ideally, the therapy should use sufficient PPI to overcome any detrimental effects of smoking.

Amoxicillin plus PPI dual therapy could also provide the base for the addition of a third or fourth drug given either as a sequential therapy or as a concomitant therapy. The dual PPI and amoxicillin component with standard doses for two weeks is expected to provide a cure rate of approximately 50%. Higher and more frequent dosing would be expected to raise the base and thus the overall success even if the success relates to the additional components remained unchanged.

Fluoroquinolones, furazolidone, rifabutin and other possibilities

Generally new drug combinations are constructed from existing formulas by substituting the new drug for the component subject to increasing resistance. Thus for triple therapy, the new drug is generally substituted for clarithromycin and in quadruple for metronidazole. The

concept is based on the premise that success requires drugs not used before. Fluoroquinolones such as levofloxacin and moxifloxacin are currently in vogue generally as a PPI plus amoxicillin plus fluoroquinolone combination. The concept of high dose, longer duration initially and if the results are good, simplify while maintaining effectiveness has generally been ignored and as meta-analyses have shown short duration fluoroquinolone results (eg, 7 days) were significantly inferior (eg, Grade F) to 10 days which itself only produced a Grade C result ⁶⁹. Unfortunately, fluoroquinolone resistance has been rapidly increasing and these drugs will likely 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 after multiple treatment failures as resistance is unlikely whereas as noted above fluoroquinolone resistance has been steadily increasing. Like bismuth, furazolidone is not available in many countries. We use furazolidone in quadruple therapy substituting for metronidazole. Furazolidone is no longer sold in the US but is readily available in Mexico.

Thinking outside the box: the use of treatment enhancers

There is considerable interest in probiotics to enhance effectiveness of antimicrobial therapy for *H. pylori* by increasing eradication rates and reducing side effects. Two recent meta-analyses suggest a modest effect ^{70, 71}. Studies are needed to identify which strains to use and what is the best delivery system to achieve reliable results. Probiotics are not inexpensive and thus cost will need to be taken into consideration, especially if the benefits are minor. Pronase and N-acetyl cysteine have been used to change the mucus layer and potentially expose the bacteria. In one trial pronase given as 18,000 tyrosine units of pronase thrice daily for 2 weeks significantly increased the effectiveness of traditional triple therapy (eg, from 76.5 to 94%) ⁷². Clearly, additional studies are needed.

Conclusions

H. pylori cause a serious transmissible infectious disease. Increasing resistance has complicated successful therapy such that what is and is not appropriate therapy must be reconsidered. Recent advances have shown how it is possible to successfully deal with both phenotypic and genetic resistance and what still needs to be done is now clearly identifiable. .

Key points

- Traditional triple therapy remains effective only when used to treat infections with susceptible organisms.
- The prevalence of antimicrobial resistance has increased such that, to maintain acceptable cure rates, all patients should be considered as having resistant infections.
- Empiric therapies that do not reliably yield 90% or greater cures, intention to treat, should not be prescribed. Triple therapies containing combinations of a proton pump inhibitor, amoxicillin, clarithromycin or metronidazole now typically yield cure rates <80% and are no longer acceptable as empiric therapy.
- Initial empiric therapy options are now between sequential therapy, concomitant 4 drug antibiotic therapy, and bismuth containing high metronidazole dose quadruple therapy.
- Sequential therapy and concomitant (4 drug 3 antibiotics) therapy have the potential to be improved by simple measures such as increasing the duration of therapy.

- Higher dose frequent proton pump inhibitor therapy can reduce phenotypic resistance and should increase the cure rates of amoxicillin-containing dual therapy into the acceptable range.

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Results of Recent Trials

Figure 1.

Results of recent comparisons studies with more than 100 patients that tested the combination of a PPI plus amoxicillin plus clarithromycin. The dotted line signifies the threshold for an 80% cure rate. The results are shown as mean cure rates (ITT) and 95% confidence intervals. The number of patients in the studies and the country where the study was done are shown within each. From references ¹⁴, with permission.

Report Card (ITT)		
Grade	Cure Rate (ITT)	Score
A	$\geq 95\%$	Excellent
B	90-94%	Good
C	85-89%	Acceptable
D	81-84%	Poor
F	$\leq 80\%$	Unacceptable

Figure 2.

Recently proposed report card for scoring the outcome of anti-*H. pylori* therapy, intention to treat. From reference ¹⁴, with permission.

Figure 3.

Weight mean and 95% confidence intervals for 16 studies of sequential therapy (n = 1805) for 10 days(modified intention-to-treat)⁵⁷ and 9 studies of concomitant therapy (n = 715) ranging from 3 to 7 days (intention-to-treat)^{59–67}.

Table 1

Current therapeutic recommendations in the era of increased clarithromycin and metronidazole resistance.

Bismuth-containing quadruple therapy

- A bismuth salt & tetracycline HCl 500 mg q.i.d., or t.i.d, plus metronidazole/tinidazole 500 mg t.i.d. plus a PPI b.i.d.

Sequential therapy*

- A PPI plus amoxicillin 1 g bid for 5 days followed by the PPI plus clarithromycin 500 mg and tinidazole/metronidazole 500 mg b.i.d. for 5 days.

Concomitant (4 drug 3 antibiotics) therapy**

- A PPI plus amoxicillin 1 gm, clarithromycin 500 mg, tinidazole/metronidazole 500 mg b.i.d., for 7 to 14 days.

High dose dual therapy***

- High dose PPI plus amoxicillin 500 mg every 6 hours for 14 days
-

See text for details.

* Sequential therapy can likely be improved to a Grade A result by increasing the duration and/or continuing the amoxicillin throughout the entire treatment period.

** 14 days is recommended. Neither sequential nor concomitant therapy is recommended as a salvage therapy. Triple therapy dose packs can be used for concomitant therapy by adding the b.i.d. tinidazole/metronidazole.

*** 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 Western populations. High dose implies that the effectiveness of acid suppression in rapid metabolizers and poor PPI metabolizers is equivalent.