Therapy for *Helicobacter pylori* Infection Can be Improved
Sequential Therapy and Beyond

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Abstract

As with other bacterial infections, successful treatment of *Helicobacter pylori* infections depends on the use of antibacterial agents to which the organism is susceptible. In this article, we use the proposed report card grading scheme (i.e. grade A, B, C, D, F) for the outcome of clinical trials, where intention-to-treat cure rates >95% = A, 90–95% = B, 85–89% = C, 81–84% = D and <81% = F. The goal of therapy is to consistently cure >95% of patients (e.g. provide grade A results). Like tuberculosis, *H. pylori* infections are difficult to cure and successful treatment generally requires the administration of several antibacterial agents simultaneously. Duration of therapy is also important and depends upon whether resistance is present; 14 days is often best. With few exceptions, worldwide increasing macrolide resistance now undermines the effectiveness of the legacy triple therapy (e.g. a proton pump inhibitor [PPI], clarithromycin and amoxicillin) and, in most areas, cure rates have declined to unacceptable levels (e.g. grade F).

The development of sequential therapy was one response to this problem. Sequential therapy has repeatedly been shown in head-to-head studies to be superior to legacy triple therapy. Sequential therapy, as originally described, is the sequential administration of a dual therapy (a PPI plus amoxicillin) followed by a Bazzoli-type triple therapy (a PPI plus clarithromycin and tinidazole) and has been shown to be especially useful where there is clarithromycin resistance. However, the cure rates of the original sequential treatment are grade B and can probably be further improved by changes in dose, duration or administration, such as by continuing the amoxicillin into the triple therapy arm. The sequential approach may also be more complicated than necessary, based on the fact that the same four drugs have also been given concomitantly (at least nine publications with >700 patients) as a quadruple therapy with excellent success.

This article discusses the approach to therapy in the modern era where antimicrobial resistance is an increasing problem and legacy triple therapy is no longer an acceptable initial choice. Methods to achieve acceptable eradication rates (e.g. grade A or B results) are discussed and, specifically, sequential therapy is considered both conceptually and practically. Suggestions are provided regard-

ing how sequential therapy might be improved to become a grade A therapy as well as how to identify situations where it can be expected to yield unacceptable results. New uses for current drugs are discussed and suggestions for subsequent randomized comparisons to overcome phenotypic and genotypic resistance are given. We propose a change in focus from comparative studies (designed to prove that a new therapy is superior to a known inferior therapy) to demanding that efficacious therapies meet or exceed a pre-specified level of success (i.e. grade A or B result). To do so, coupled with less concern about the effect of recommendations on the pharmaceutical industry, should provide clinicians with much higher quality information, and improve the quality of medical care and recommendations regarding treatment. Ultimately, there is little or no justification for comparative testing that includes an arm with known unacceptably low results. *H. pylori* gastritis is an infectious disease and should be approached and treated as such.

Fundamentally, *Helicobacter pylori* is a bacterial pathogen that causes gastroduodenal inflammation. *H. pylori*-induced chronic gastroduodenal inflammation leads to alterations in the structure and functions of the stomach and proximal duodenum, and may result in clinical outcomes such as duodenal ulcer disease, gastric ulcer disease and atrophic gastritis. Atrophic gastritis may then lead to iron and/or vitamin B_{12} deficiency, gastric adenocarcinoma and/or primary B-cell gastric lymphoma.[1-4] *H. pylori* infections are typically acquired in childhood with clinical manifestations occurring after a latent period that may span many decades. Like other serious chronic infections with long latent periods (e.g. syphilis and tuberculosis), men are more likely to experience the serious consequences.[5] However, the proportion of those infected that go on to develop recognizable clinical syndromes is higher (approximately 20%) than with infections with *Mycobacterium tuberculosis* or *Treponema pallidum*.[5,6]

As with other bacterial infections, successful treatment is primarily dependent on the use of antibacterials to which the organism is susceptible. Like tuberculosis, the infection is difficult to cure and successful treatment generally requires several antibacterials to be administered simultaneously. In addition, because *H. pylori* typically inhabits an acidic environment, suppression of gastric acid secretion is needed for the acid-susceptible antibacterials to have maximum effectiveness and possibly to overcome phenotypic resistance.[7] Treatment failures

that are not explained by failure to take the medications are typically caused by phenotypic or acquired resistance.[8,9] Taking a lead from the lessons learned from the treatment of tuberculosis, one can surmise that treatment failure that is not associated with the presence of acquired antibacterial resistance (i.e. phenotypic resistance) is primary evidence of problems related inadequate duration, dose or both.[7,10] One basic rule regarding therapy for infectious diseases including *H. pylori* is "the best therapy is one that cures the infection in all patients, in all geographic regions, irrespective of the requirements regarding dosing intervals, number of tablets, or duration".[9] The most commonly used therapies are either legacy triple therapies consisting of a proton pump inhibitor (PPI) and two antibacterials (chosen from amoxicillin, metronidazole or tinidazole [which are thought to be interchangeable], and clarithromycin), or a bismuth-containing triple therapy consisting of bismuth, metronidazole and tetracycline (BMT).[11-14] The single most widely used and widely approved therapy, and the one most strongly supported by the pharmaceutical industry, is a triple therapy consisting of the combination of a PPI, amoxicillin and clarithromycin (PPI-AC). Over time, the success rates with this therapy have fallen parallel to the increase in clarithromycin resistance, such that the initial high success rates that were achieved are usually no longer obtainable. The exception is in countries, such as Sweden, where clari-

thromycin resistance has remained low as a result of the low usage of macrolides.[15]

1. Expected Outcomes of *Helicobacter pylori* Therapy

Assessment of the outcome of *H. pylori* treatment differs in many regards from that of other infectious diseases because, typically, outcomes of comparative clinical trials have been assessed as the same, better or worse in relation to another therapy (e.g. legacy triple therapy), irrespective of whether that 'gold standard' met or exceeded a predetermined and objective measure of outcome such as a ≥90% cure rate; frequently the gold standard used is actually brass. This approach has resulted in therapies with unacceptably low cure rates being described as equivalent or equally good, instead of identifying both treatments as being unacceptable because of the low cure rates.[16,17].

The definition of an acceptable result has been discussed for many years. For example, in the mid-1990s, it was suggested that only regimens that achieved a cure rate of 90% should be used in clinical practice.[18-20] In 1997, the breakpoint between an acceptable and unacceptable therapy was defined by the Maastricht conferences as an intention-to-treat (ITT) eradication rate of >80%.[21] This was a very low expectation. It is impossible to know whether, or if so by how much, the conference sponsor influenced this decision. Clearly, in our opinion, their sales might be directly affected by the level of the cut-off value. The original Maastricht conference was followed by a number of country-specific or region-specific sponsored 'consensus conferences' and some of the original Maastricht participants were frequently invited to participate. Indeed, the pharmaceutical companies that market PPI-AC combinations continue to sponsor events at conferences and entire conferences, and invite and reward 'opinion leaders'. However, the fact that the breakpoint recommended did not increase to the expected 90% can not all be blamed on industry sponsors, as there are many other potential factors that have been overshadowed by the fact that the

initial excellent results have not been sustained (e.g. see figure 1).[17,22-40]

By the time of the Maastricht III conference, the data that legacy triple therapy was becoming ineffective was beginning to become conclusive. However, the results with sequential therapy were just becoming available and then only from Italy. Data regarding the efficacy of sequential therapy in the face of resistance was still not available and sequential therapy was, and is still, not approved by any regulatory body. The Maastricht III consensus was that legacy triple therapy was the preferred initial choice for *H. pylori* treatment, provided that the rate of clarithromycin resistance was <10–20%. This was clearly an indirect and somewhat vague statement, and, in retrospect, provided little actual assistance for physicians since the prevalence of clarithromycin resistance is generally unknown to them (i.e. an expert would understand the ramifications but the practicing physician would not). Of additional interest with regard to the Maastricht III conference, the primary industry sponsor of the conference, which sells both clarithromycin and esomeprazole, taped the conference and within a few months produced two very similar books[42,43] (in Italian) regarding the management of *H. pylori* infections
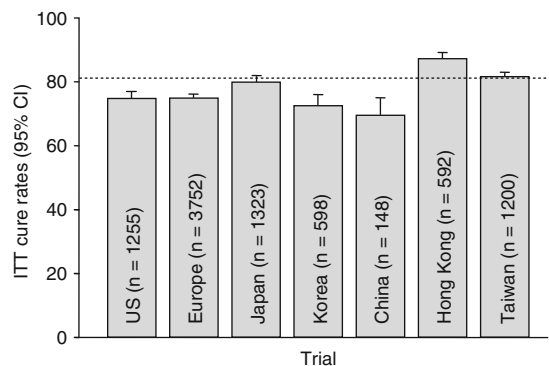

Fig. 1. Results of recent comparative studies with >100 patients that tested the combination of a proton pump inhibitor plus amoxicillin plus clarithromycin. The dotted line signifies the threshold for an acceptable result. The results are shown as mean cure rates (intention to treat [ITT]) and upper limits of 95% confidence intervals. The number of patients in the studies and the country where the study was performed are shown within each column (reproduced from Graham et al.,[41] with permission from Blackwell Publishers Ltd).

that provided details of the conference and were provided free to Italian physicians.

One conundrum facing all those who have been tasked with providing recommendations for *H. pylori* treatment has been that if legacy triple therapy is no longer effective (except in a few areas), what should be recommended? This is compounded by the fact that in many countries, legacy triple therapy is the only option approved by regulatory authorities and the alternate bismuth-containing quadruple therapy is not available in many areas. We believe that the data are clear; legacy triple therapy should be abandoned, except in areas where it is proven to be effective (grade A or B results) [see figure 2] or its use is based on pretreatment susceptibility testing. The issues of how to deal with conflicts and potential conflicts of interest are beyond the scope of this article. Instead, this article deals with ideas about how to improve *H. pylori* therapy and the communication of the results.

H. pylori gastritis is an infectious disease and clinicians typically demand cure rates >95% for bacterial infectious diseases. Probably the most thoughtful discussion of the approach to defining outcome was by Hopkins[44] in 2001. Hopkins provided recommendations for defining equivalence and efficacy. To be considered efficacious required that the lower 95% confidence interval for the point estimate (percentage of patients cured) remain >80%. Unfortunately, these recommendations were

not generally followed. Recently, based on expectations with other infectious diseases, we proposed a simple and, we believe, intuitive grading system (i.e. grade A–F) or report card for treatment regimens with cut-off values suggested for both ITT and per protocol (PP) results (figure 2).[41] We proposed that clinicians should only prescribe therapies that locally provided grade A results (ITT and PP cure rates at least 95%). If not obtainable, grade B therapies should be prescribed; grade F therapies (ITT and PP cure rates <81% and ≤85%, respectively) should be avoided. We believe that to consider *H. pylori* as just another infectious disease would lead to a change in focus and prevent treatment being declared successful when one achieved what are actually unacceptably low cure rates[17] or when comparative, randomized controlled trials (RCTs) against known inferior therapies are performed.[16,45-47] It remains to be seen whether this approach will be successful and, if so, how long it takes.

2. Overcoming the Problem of Resistance

Metronidazole resistance is not an 'all or none' phenomena. For example, the addition of a PPI, a higher dose of metronidazole, or preferably both, results in the partial reversal of the reduction in effectiveness of BMT in patients with metronidazole-resistant *H. pylori*.[48] In contrast, clarithromycin resistance is typically 'all or none' such that resistance converts triple therapy into a dual therapy.[9,49,50] With few exceptions, macrolide resistance has increased to the point that it has undermined the effectiveness of the legacy PPI-AC triple therapy. This is reflected in the fact that in most advanced countries, the cure rates have fallen and, typically, PPI-AC therapy is now scored as unacceptable (i.e. a grade F regimen) [figure 1].[17,22-40]

The development of sequential therapy was one response to this problem and has repeatedly been shown in head-to-head studies to be superior to legacy triple therapy.[11,46,51] However, the results (ITT) for sequential therapy are generally near the lower end of grade B (cure rates of 90–94%) and not the desired grade A result. This article discusses

Report card (ITT)		
Grade	Cure rate (ITT)	Score
A	≥95%	Excellent
B	90–94%	Good
C	85–89%	Acceptable
D	81–84%	Poor
F	80%	Unacceptable

Report card (PP)		
Grade	Cure rate (PP)	Score
A	≥95%	Excellent
B	90–94%	Good
C	86–89%	Poor
F	≤85%	Unacceptable

Fig. 2. Grading scale for *Helicobacter pylori* therapy. (**a**) Report card for scoring the outcome of anti-*H. pylori* therapy, intention to treat (ITT). (**b**) Report card for scoring the outcome of anti-*H. pylori* therapy, per protocol (PP) [reproduced from Graham et al.,[41] with permission from Blackwell Publishers Ltd].

sequential therapy and the alternatives, and provides suggestions regarding how sequential therapy might be improved to become a grade A therapy. We also identify situations where sequential therapy is expected to yield unacceptable results. We suggest ideas and combinations that are options for pilot studies and for randomized clinical trials to test new ideas and therapies against sequential therapies.

The overall goal of therapy of an infectious disease is to consistently yield grade A results. Many clinical investigators have accepted the RCT as a new religion when it is actually limited to asking specific types of questions. The primary purpose of RCTs is to compare therapies, identifying equivalent as well as better therapies. Generally, when placebo controls are unethical, the gold standard should be the 'best available'. This best available standard has often been ignored in RCTs considering *H. pylori* treatments, resulting in conclusions where equally bad therapies were actually recommended to be used.[52] Clearly, the fact that a regimen is 'approved' or 'recommended' does not meet the obligations of the clinician to the patient or to society.[53] In many instances, the RCT is an inappropriate format, especially if it includes a component that is a known inferior therapy (*vide infra*). For example, 10 years ago, we wrote "another approach has been for investigators to compare a known poor therapy (e.g. PPI plus amoxicillin) with a known good therapy (a PPI triple therapy) to 'prove' that the known poor therapy is actually poor. In reality, there is little justification for entering patients into a study when it is known beforehand that one of the therapies is inferior".[9]

Typically, the sequence for identifying a new or improved regimen is to do one or more small pilot studies to identify and refine a target therapy that appears as good or better than the best available (e.g. provides grade A results).[54] This is then followed by a larger RCT to confirm equivalence or superiority to the best available. It would be difficult, but not impossible, to compare the new excellent therapy against a proven inferior one (e.g. legacy triple therapy) in a RCT. An ethical study would be necessary to provide truly informed consent, including all known relevant data that might affect whether new patients would enter or ongoing patients would continue. It would also require full disclosure to the editors and readers regarding what was told to the patients and the trade-offs used to make the therapy acceptable (e.g. all patients were followed and retreated with eradication confirmed). Unfortunately, the comparative studies of sequential and triple therapy have remained silent with regards to the whether truly informed consent was given.[46]

Repeatedly, an RCT may also be an inappropriate choice. For example, to answer whether the proven effectiveness of a particular therapy is related to its ability to obtain high cure rates in the presence of antimicrobial resistance would not require a control group if the effect of resistance on the alternate therapy was already known. Instead, a trial of the new therapy would need only to compare its results in antimicrobial-susceptible and -resistant infections. If an RCT was desired, one could imagine comparing the new therapy with modifications designed to possibly improve the outcome (e.g. different durations of treatment) and to extract the resistance data from both arms.

3. Sequential Therapy

Sequential therapy, as originally defined, is the sequential administration of a dual therapy (a PPI plus amoxicillin) followed by a Bazzoli-type triple therapy (a PPI plus clarithromycin and tinidazole).[55] Each regimen is used for 5 days leading to a total duration of 10 days. Recent studies that included antimicrobial susceptibility tests are consistent with the notion that the superiority over legacy triple therapy is primarily due to improved outcome with clarithromycin-resistant strains (e.g. sequential and legacy triple therapy appeared equivalent with clarithromycin-susceptible strains).[35] However, sequential therapy failed in the presence of dual clarithromycin and metronidazole resistance, and therefore is likely to be an unacceptable choice in regions where both clarithromycin and metronidazole resistance are common. There is also the question about whether it is unnecessarily complex

in regions where dual resistance to metronidazole and clarithromycin are rare.[11]

4. Sequential Therapy in Practice

The initial descriptions of the sequential therapy combination did not describe the full rationale for the combination or for the decisions regarding choices of dose and duration. Thousands of patients were tested with many legacy triple therapy failures before the hypothesis was confirmed that the superiority of sequential therapy was due to its improved results in the presence of clarithromycin resistance.[11] The comparator was PPI-AC, which had repeatedly been shown to have a low cure rate in Italy.[11,25,56] Although some minor variations of sequential therapy were evaluated, one would have preferred to see experiments designed to achieve even better results and to examine new hypotheses. For example, as noted in section 2, the triple therapy comparator for sequential therapy was not that used in sequential therapy (i.e. PPI-AC instead of PPI plus clarithromycin and tinidazole) and the obvious comparison of sequential versus a Bazzoli-type triple therapy has not yet been done.[11]

The sequential regimen also calls for the amoxicillin to be discontinued after only 5 days. Why? There are a number of reasons to suggest that the outcome might be further improved had the amoxicillin been continued throughout the entire treatment period. For example, there are at least nine studies using all four drugs concomitantly (i.e. concomitant therapy consisting of an antisecretory drug, an imidazole, a macrolide and amoxicillin) that have reported excellent results with 3–7 days of therapy (*vide infra*).[57-65]

In summary, the published studies with sequential therapy conclusively and repeatedly demonstrated its superiority to legacy triple therapy in Italy, but left us with questions about how to improve it to consistently achieve grade A results. However, we are left puzzled about (i) whether sequential therapy is superior to a Bazzoli-type regimen without the PPI-amoxicillin run-in period; (ii) the effect of continuing the amoxicillin into the triple therapy arm as a concomitant quadruple therapy; and (iii) whether the results would be improved by increasing the overall duration. Finally, the past experience with concomitant therapy suggests that the sequential approach may be more complicated than is actually necessary (i.e. whether giving all four drugs as a concomitant therapy would provide equal or even superior results). Details regarding these questions are discussed in the following sections.

5. Thinking About the Concept of Sequential Therapies

The sequential administration of antibacterials is generally not recommended because of the fear of promoting drug resistance. However, the dual therapy used in sequential therapy utilizes drugs that rarely result in resistance, such that the outcomes should be either cure of the infection or a marked reduction in bacterial load, making the presence of a pre-existing small population of resistant organisms less likely.[50,66] This concept was one basis for the use of bismuth with the initial therapy, eliminating most of the organisms, and then the addition of a second, third and even fourth drug killing the few remaining organisms leading to a high cure rate.

Sequential therapy starts with the dual therapy of a PPI and amoxicillin, making sequential therapy a dual-based triple therapy. Dual therapy has a long history and there are numerous studies from which to make reasonably sound predictions regarding its use and the effects of changes in dosage and/or duration. The outcome in PPI plus amoxicillin dual therapy is duration (e.g. 14 days) and dose (2 g of amoxicillin) dependent, and is adversely affected by smoking.[67] A study of this combination in Italy recently confirmed the older data as it yielded the expect approximate 50% cure rate suggesting that one can still rely on the results of prior experiences.[31] The effectiveness of dual therapies can be further improved by increasing the amount of acid suppression, for example, omeprazole 40 mg and amoxicillin 750 mg given three times daily for 14 days has reported eradication rates ranging from 67% to 91%.[68-71] Our recent experience with the higher dose approach has yielded a cure rate in the range of 70–75% and formed the basis of our ap-

proach to a new sequential therapy.[72] As a general principle, whenever the outcome of a PPI-containing therapy is better in poor PPI metabolizers compared with rapid or normal PPI metabolizers, one can reliably predict that changes in the dose or administration interval of the PPI will consistently produce an overall better outcome.[73,74] Giving the PPI and the amoxicillin every 6 hours has provided consistently high cure rates and we believe that it is time for dual therapy to undergo a revival.[75]

6. Understanding the Effect of the Components of Sequential Therapies

In order to think about the results of multidrug therapies, it is often useful to make simple models that express the effect of a sequential therapy based on the expected results with the combinations of the components. The results of different dual therapy combinations, such as a PPI plus amoxicillin, clarithromycin or metronidazole, were established long ago, such that the expected changes associated with different doses and durations of these combinations, are available and can be used to examine whether they coincide with the actual outcomes.[67,76-80]

The cure rate with 5 days of the dual therapy component of sequential therapy would be expected to be low (e.g. approximately 25%). This expectation was confirmed by the failure of sequential therapy in the presence of dual resistance, which indirectly examined the effect of the 5-day dual therapy component. As noted in section 2, extending the duration of the dual therapy arm or continuing the amoxicillin into the second phase would be expected to result in a better overall outcome.

The simple model we describe here assumes that the duration of therapy is 14 days, either as 14 days of dual therapy or with the amoxicillin being continued into the second phase. As noted in section 5, the results with the dual therapy (PPI plus amoxicillin) are known to be both dose and duration dependent, and are negatively affected by smoking. The example shown in figure 3 assumes a cure rate of 50% for the 14-day dual therapy and an 80% cure rate for the triple therapy component. Thus, the cure rate per 100 patients would be the result of the dual therapy
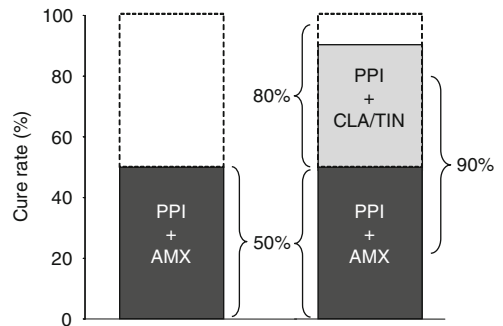

Fig. 3. Theoretical results with sequential therapy. Model showing the outcome of sequential therapy considered as a dual therapy (proton pump inhibitor [PPI] plus amoxicillin [AMX]) followed by a triple therapy (PPI plus tinidazole [TIN] and clarithromycin [CLA]). In this model, the total duration of the AMX + PPI arm is 14 days and the cure rate of the dual therapy is 50%. The 80% cure rate with the triple therapy is related to the presence of CLA resistance in the population. Clearly, improving the effectiveness of either arm (e.g. increasing the dose and frequency of the PPI would improve the overall outcome). The overall outcome in this model would be 50% + 40% = 90%.

plus the result of the triple therapy (i.e. 50% + [80% of the remaining 50 patients] or 50% + 40%), giving a 90% overall cure rate (figure 3). Increasing the dose of the PPI would be expected to increase the cure rate of the dual therapy to at least 70% and improve the outcome to 70% + 24% (80% of the remaining 30 patients), to give a total of 94%.

These hypothesis-generated experiments can provide the starting point for designing RCTs and point the way to other trials based on the study of any clinical activity (e.g. changes in doses, administration intervals, duration and formulation), which is expected to increase the cure rate of either one or both components to improve outcome. It also suggests that activities, such as smoking, or antimicrobial resistance, which are expected to reduce effectiveness should be considered for stratification in the randomization process.[65]

The results of the decision to use all four drugs concomitantly as a quadruple therapy, containing three antibacterial agents (amoxicillin, clarithromycin and metronidazole) and a PPI, can also be modelled. One approach would be to model the expected outcome from this quadruple therapy as the sum of a dual and three currently used triple therapies. For example, if one achieves a 50% cure

rate with the PPI plus amoxicillin and a 75% cure rate with each of the three triple therapies (i.e. a PPI plus amoxicillin plus clarithromycin, amoxicillin plus tinidazole, and clarithromycin plus tinidazole) would yield an overall cure rate of >99% (i.e. 50% + 37.5% + 9% + 3%). If one used a more conservative estimate with each combination achieving a 50% cure rate, the overall cure rate would fall to approximately 93% (i.e. 50% + 25% + 12% + 6%). Clarithromycin resistance would eliminate two combinations and produce a lower cure rate (PPI plus amoxicillin, and PPI plus amoxicillin plus metronidazole), ranging from 75% to approximately 90%. The choice of the starting point could also vary (e.g. PPI plus clarithromycin instead of PPI plus amoxicillin) and one gets the same results. These simple exercises provide a simple way of thinking and can be made as complicated as one wishes (e.g. to model synergy). The models are only useful if the results mirror clinical results. We propose that this type of exercise is useful for hypothesis generation and for helping design the 'next experiment' as it rapidly identifies areas where data are unknown and the experiments needed to address what really happens *in vivo*.

7. Cost Considerations

Cost effectiveness is an important consideration for any therapy. However, cost cannot be considered separately from effectiveness. The approach to simplifying therapy for an infectious disease is first to identify an effective therapy (e.g. grade A), and then to perform studies to simplify it and reduce costs. The critical element is that simplification and cost savings must be based on maintenance of effectiveness. To do a cost-effective analysis for an ineffective therapy (e.g. grade D or F) makes no sense. When cost effectiveness is discussed in relation to *H. pylori* treatment, the discussion is often one of 'cost ineffectiveness'. Repeatedly, cost effectiveness is presented in terms of the direct costs of the therapy (e.g. drugs, or drugs and procedures), which is relatively easy to calculate but is only important when the choices are equivalent in terms of (high) success rates. The most important costs are the costs

of failure, such that small gains in effectiveness (e.g. from a grade B to a grade A therapy) may provide major cost advantages based on the reduction in the costs of follow-up, retreatment, subsequent development of clinical outcomes (e.g. gastric atrophy, peptic ulcer, gastric cancer and transmission to others), lost time from work and quality of life. These are difficult to measure and thus often ignored. The cost of the drugs used is rapidly becoming less of an issue as all the drugs currently used to treat *H. pylori* are either off-patent or soon to be off-patent, such that the drug cost component of overall costs is, or will soon become, minimal.

8. Concomitant Therapy

In 1998, Treiber et al.[64] and Okada et al.[62] both reported studies using an antisecretory drug, a macrolide, an imidazole and amoxicillin concomitantly for 5 days with ITT eradication rates of >90%. Subsequent experiments by these authors and others confirmed these observations, and there are now data on >700 patients available (figure 4).[57-65]
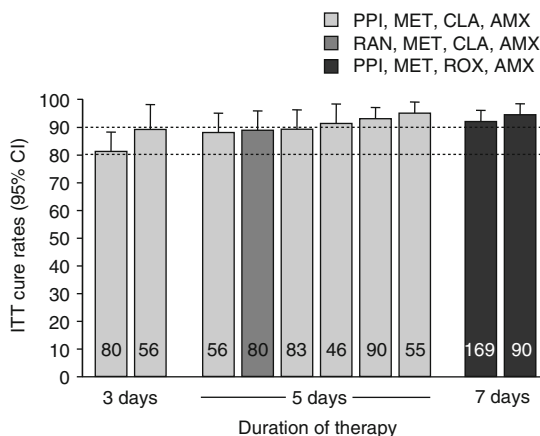

Fig. 4. Summary of studies of concomitant therapy. The results are shown as mean cure rates (intention to treat [ITT]) and upper limits of 95% confidence intervals of studies of concomitant therapy consisting of an antisecretory drug, an imizadole, a macrolide and amoxicillin (AMX) for 3, 5 or 7 days.[57-65] Not shown are comparisons where the antisecretory agent was ranitidine bismuth citrate, which yielded cure rates of 94.6% (n = 56) with a 3-day therapy and 90% (n = 80) with a 5-day therapy.[57] Numbers in the columns represent the number of patients in each study. **CLA** = clarithromycin; **MET** = metronidazole; **PPI** = proton pump inhibitor; **RAN** = ranitidine (300 mg twice daily); **ROX** = roxithromycin.

There are also randomized studies confirming the superiority of concomitant therapy to legacy triple therapy.[57,59,61] This approach as been evaluated for 3, 5 and 7 days with good results (figure 4). Outcome has been better with poor PPI metabolizers, which is consistent with the concept that concomitant therapy could be further improved by alterations in PPI dose and possibly duration of therapy.[81] Studies comparing sequential and concomitant therapy are currently in progress.

9. Recommendations

Ideally, a drug combination could always be chosen that avoids giving antibacterials to which the organisms are already resistant and that reliably provides cure rates of 95% or greater. However, community-wide levels of antimicrobial resistance are generally not available for *H. pylori* and pretreatment antimicrobial susceptibility testing is not currently practical as only a few laboratories are prepared to provide the services required. Therefore, clinicians are frequently forced to make empirical choices. BMT quadruple therapy remains highly effective in many areas provided that sufficient doses, especially of the imidazoles, are given and duration is at least 14 days, and this should remain be a preferred approach. Sequential therapy showed that significant improvements in cure rates may be obtainable with current drugs. However, the results with the current sequential protocol are overall grade B and studies, such as those evaluating dose, duration and various combinations, are needed to test whether it can be improved to a grade A regimen. However, in areas with a high prevalence of dual metronidazole and clarithromycin resistance, the current formulation of sequential therapy is likely to provide grade F results; thus, new drugs or drug combinations are needed. While it is clear that we should abandon legacy PPI plus clarithromycin and amoxicillin therapy as a primary empirical therapy in most Western countries, it also appears likely that this combination can be resurrected by the simple addition of metronidazole or tinidazole to transform it into a triple-based quadruple therapy (concomitant therapy).

One suggestion for exploring sequential therapy is to continue the amoxicillin for the final 5 days to yield a dual-based quadruple therapy. Such a simple change may well improve the outcome to a grade A therapy; however, a longer total duration of therapy, different doses especially of the PPI and/or different frequencies of administration also deserves detailed study. In regions where resistance is a growing problem, one can theoretically substitute drugs, such as tetracycline, a fluoroquinolone or furazolidone, for clarithromycin and/or metronidazole or tinidazole.

Future studies can be more efficient if investigators recognize that comparisons against known ineffective regimens are unnecessary, and, when done, require extensive disclosure and documentation so as not be unethical. Abandoning comparisons to inferior combinations will free up many hundreds of patients for testing new hypotheses. Results with a new therapy should be reported in relation to the results of pretreatment susceptibility testing. This alone will markedly increase the interpretability of the results, as well as the number of questions that can be asked and the comparisons that can be made. A change in focus from studies designed to prove that a new therapy is superior to that of a known inferior therapy to meeting pre-specified efficacy standards (i.e. requiring a grade A or B result) will provide clinicians with much higher quality information, and should improve medical care and the quality of recommendations. This must also be coupled with elimination of the concern about the effects of the recommendations on industry. Ultimately, there is little or no justification for comparative testing that includes an arm with known unacceptable cure rates. *H. pylori* gastritis is an infectious disease, and should be approached and treated as such.

Acknowledgements

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