Personal viewpoint

A reliable cure for *Helicobacter pylori* infection?

There are significant benefits to be gained by treating *Helicobacter pylori* infection, particularly in patients with peptic ulcer disease. Once a physician makes a decision to begin treatment, he/she immediately wants to know how. I am often asked which drugs and drug combinations are effective, how to draw conclusions from the treatment trials, and which protocols are best. One common question is 'How many drugs and for how many days?' While I do not believe that either 'how many' or 'how long' are important and they may not even be relevant, the answers are certainly controversial. The goal of treatment is simple, to cure the infection and not 'eradicate the patient'. Large multicentre clinical trials comparing treatments are virtually non-existent. The current recommendations are often based upon summary data put together by opinion leaders based upon information obtained from small clinical trials often published only in abstract form. We now have a number of regimens that will reliably cure most *H. pylori* infections. Initially, we proposed that the clinicians use an 80% rule – that is, they would only choose treatments that had a success rate of at least 80%.¹ Now, it seems we can move forward to a 90% rule.

Terminology of treatments and results of therapy

Anti-*H. pylori* treatments are called monotherapy, dual therapy, triple therapy, quadruple therapy, etc, based on the number of drugs given. We have come to recognise that the goals of anti-ulcer therapy include healing the ulcer and curing the infection.² To properly name a therapy you should not simply count drugs but rather count those that are integral to the anti-*H. pylori* objective. As co-administration of H₂ receptor antagonists with standard triple therapy has little or no effect on the results, triple therapy with an H₂ receptor antagonist to assist in accelerating ulcer healing is called triple therapy whereas omeprazole plus amoxicillin is called dual therapy because omeprazole is required for reasonable cure rates.

Before we recognised that we were dealing with an infectious disease, gastroenterologists made up their own terminology and began to 'eradicate' *H. pylori*. While we have eradicated small pox infection from mankind, we normally do not tell the patient that we have eradicated their pneumococcal pneumonia, their venereal disease, their urinary tract infection, or any other infection. Instead, we tell them that the infection was 'cured' or that 'the treatment was successful'. Eradicate is a 'bad' word but it may be too firmly entrenched into the lexicon of *H. pylori* ever to be replaced. If you pay attention, you will find that speakers commonly announce that they have 'eradicated 50% of their patients'. While it is true that if we eradicate our patients, we cure disease, it would be better to cure the infection and cure the disease. We need to eradicate 'eradicate'.

How to make a decision about which drugs and what duration

For a treatment to be judged successful it must not only cure the infection in a controlled environment, but must also have similar results in the clinic. The patients must be willing to take the drugs; significant side effects must be

infrequent or mild. The importance of compliance is the one area where everyone agrees poor compliance equals poor results. Physicians generally believe that compliance is better when the frequency of the administration is reduced. Thus, twice a day doses might be superior to three times a day or to four times a day. In almost all the clinical trials, however, compliance has been excellent irrespective of the regimen. Whether the high compliance rates achieved with the multidose regimens relate to patient education, which accompanies the prescription of these drugs, or the intense desire of the ulcer patient to obtain a cure, is unknown.

Will reducing the duration of treatment improve compliance? Probably, but such 'improved compliance' may be irrelevant and potentially harmful if there is a lower cure rate with shorter treatment. For example, if the infection is cured after three days of treatment, any additional therapy is unnecessary. Thus, the rate of success for the treatment will depend on the compliance rate during the period when cure occurs. If the cure rate is best with two weeks of treatment, good compliance for one week is not enough. Similarly, if one week is enough, the success rate for two weeks of treatment cannot be worse even if the compliance is poor during the second week of treatment.

Evaluation of trials of antimicrobial treatment for *H. pylori* infection

Most of the available data come from small clinical trials. To judge whether you can apply that data to your own patient population you must look at the population of patients treated, the results achieved (proportion in whom the infection was cured), and the sample size.

The first approach to deciding if a therapeutic regimen is potentially useful is to carefully review the results of the clinical trials that have been published and ascertain whether the results are relevant to the patients you see. For example, someone may report excellent results with a metronidazole containing triple therapy but, if our population is one where metronidazole resistance is present in 80%, we would not expect excellent results. What we want is an estimation of how likely that the regimen will be successful in our population. What we actually want is confidence intervals.

Use of 95% confidence intervals to estimate effectiveness

The use of 95% confidence intervals is a wonderful measurement for the clinician.³ It provides an estimation of the range that a result could reasonably fall into if the study were repeated with the same or a similar population. It provides us the estimate we want. It also tells us what the result is not likely to be. For example, if a study of 600 patients showed a cure rate of 60% with 95% confidence intervals of 56% to 64%, we would know that if the study was repeated, the cure rate would have a 95% chance of falling within that range and not be a value outside of those confidence limits. Only one time in 20 would the result be expected to fall outside of the 95% confidence intervals. In this instance, if we demand an 80% cure rate, and 80%

Effect of sample size on 95% confidence intervals is shown both in tabular and graphic forms illustrating that the range narrows as the sample size increases with the most rapid decrease being between one and approximately 30 patients entered.

is not included within the confidence intervals, we can reasonably abandon that treatment.

Let's explore some clinical data. In our example we will construct a theoretical study that ultimately yields a cure rate of 70%. In this study, the first three patients are cured; the cure rate is 100%. You might rightfully say, no one would report three patients because we intuitively know the results could end up with almost any cure rate (the 99.9% confidence interval is 8% to 100%). The results of studies with 10 to 12 patients are often published in abstracts, and in this example, the cure rate was nine of 10 (the 95% CI is 55.5% to 99%). With 20 patients, the cure rate fell to 85% (95% CI=62% to 97%). At 50 the cure rate was 80% (95% CI=66% to 90%). After 200 patients, we find that 74% are cured (95% CI=67% to 80%). At the end of the study of 600 patients, 70% are cured (95% CI=66% to 74%). We can see this happening in the Figure, when we see that the confidence intervals narrow as the sample size increases and that the rate of change is very steep until a sample size of about 30 to 40 is obtained. The rate of change then flattens out. The lessons include: to estimate the usefulness of a treatment we must pay at least as much attention to the 95% confidence intervals as to the reported proportion cured, and a sample size of around 30 is the minimum to evaluate a treatment with a good result. It must not be forgotten that the exact 95% confidence interval is not 'exact' and that one time in 20 the results will be outside those limits. Failure is easier to identify. For example, one cured of 10 yields 95% CI of 0% to 44%; additional patients are not needed to discard the treatment.

In reality, because we are only interested in treatments that yield cure rates of 90% or greater (if you prefer, 80% or greater), we need only to look at the 95% confidence intervals for sample sizes that surround this region. The Table shows the 95% confidence intervals for different sample sizes that achieved cure rates of 90%, 95%, or 100% and illustrates the wide range in lower limits with smaller sample sizes.

Choosing the best *H. pylori* treatment

Confidence intervals are a good tool to allow us to estimate the reliability of a treatment but a different approach is required to choose between several different therapies. Recently, de Boer *et al* published a lovely study where they

95% Confidence intervals for different sample sizes with cure rates of 90% to 100%

Sample size	90% cured	95% cured	100% cured
10	55%–99%	62%–99%	69%–100%
20	68%–98%	75%–99%	83%–100%
30	73%–97%	80%–99%	88%–100%
40	76%–97%	83%–99%	91%–100%
50	78%–96%	85%–99%	92%–100%
100	82%–95%	88%–98%	96%–100%

gave triple therapy for either one or two weeks.⁴ They reported that the success rate after one week was 95% and after two weeks was 94%. They concluded that treatment for one week was as good as for two weeks and recommended one week's therapy. The study had 111 patients, was randomised, all patients were accounted for (only two were lost to follow up), and the 95% CI were given. The exact confidence intervals for their results are: for one week's therapy 85.1% to 98.8% and for two weeks' therapy, 84.3% to 98.8%. What can we learn and conclude from the study? Can we be confident that one week's therapy is equal to two weeks' therapy? Have they asked the question we are interested in? We can look at the study to ask how effective triple therapy was and as a comparison between two treatments. The study confirms previous findings that standard triple therapy is an effective treatment. The 95% confidence intervals tell us that we should expect good results in our patients. Looked at as a comparison of two studies we find that the treatments are not statistically different and the confidence intervals overlap, as a general rule of thumb, which suggests that they will not be statistically significantly different; in fact, the two tailed p value is 1.0. Physicians repeatedly are told that not statistically different does not mean identical. The proper analysis to ask what difference is possible is to calculate the 95% confidence intervals for the difference. This is another sample size dependent result and in this instance is –8.9% to 8.3%. As the probability for any one result within the 95% confidence intervals is not equal values towards the extreme are less likely. Thus, worst case scenario, which would yield differences of more than 8%, is very unlikely.

There are few studies evaluating the duration of standard triple therapy of less than 14 days so comparison of the results achieved by de Boer *et al* are difficult.⁴ You are usually most influenced by your own results. We studied 22 patients with triple therapy for 10 days and achieved a 77% cure rate 95% CI=58% to 94%.⁵ It is also important to note that we used less metronidazole and a different form of bismuth again illustrating that although the words 'triple therapy' are standardised, the treatments are not.

What we want to know is better asked by designing the trial to ask if the difference between treatments was of a magnitude that we would consider clinically significant (that is, we would not use the shorter duration of treatment if the difference was confirmed). You can then easily look at the characteristics of a trial that would detect that, or greater differences, and see if the trial in question measures up to what we might have designed. While you can use confidence intervals to choose the sample size,⁶ it is generally easier to use one of the readily available computer programs (for example, SigmaStat, Jandel, San Rafael, CA) to do it for you. The data suggest that triple therapy given for two weeks would yield a 95% cure rate. For this exercise we decided that we definitely would not use a one week therapy if it yielded 85% cure rate or less. This 10 per cent difference is within the possibilities that we have already seen by examining the 95% confidence intervals from the de Boer trial.⁴ We make the assumption that we will use a p value of 0.05 and a power of 0.8. A power of 0.8 means we would have an 80% chance of detecting the difference we declared clinically significant. A power of 0.9 would be better, but we want to keep the sample size as small as we can. Almost instantly, the computer tells us that the sample size of patients completing the study for each group must be 160. Would we use one week therapy if the results were 95% *v* 90% in favour of two weeks? The sample size for that comparison (5% difference) is 474 per group, a number so large that a multicentre study would be

required. Actually, we could possibly reduce the sample size somewhat by doing one tailed tests of significance. As noted earlier, two weeks of treatment cannot be worse than one week and, thus, a one tail test should be appropriate. Even if we go to all this trouble we will then decide how to take into account the problem of metronidazole resistance, which can theoretically complicate our study as the cure rate may be lower in patients with metronidazole resistant *H pylori*.

Although the study concluded that one week therapy was equal (not significantly different) to two week therapy, the study was not designed to detect if there was a difference between one week and two weeks of treatment. Are there other pieces of information that might help us make the decision about duration of treatment? The results of the omeprazole-amoxicillin studies suggest that cure rates with 14 days of treatment were better than with 10 days or with seven days⁷ but that is a different combination. We should ask ourselves, what are the disadvantages of prescribing the drugs for 14 days? Cost and side effects are the main concerns. While duration is directly related to cost there are few data to suggest that it is an important concern in relation to side effects. As noted, improved compliance is not an issue if one week therapy is sufficient. We found that when antisecretory treatment was stopped after one week, some patients returned complaining of a recurrence of ulcer pain.⁸ In the de Boer *et al*⁴ study there was significantly higher frequency of stomach pain in those receiving triple therapy and antisecretory treatment for one week compared with two weeks (20% *v* 11%) but it is not clear if this was the result of a shorter duration of antisecretory treatment and with triple therapy antisecretory and antimicrobial treatment can be separated.

Recommendations

The goal of treatment of *H pylori* infection is to have an effective therapy with a low frequency of side effects. If the treatment fails, we also want a low frequency of acquired resistance to the antimicrobial treatment. We would prefer our antimicrobial treatment to be as specific as possible to prevent the development of antibiotic resistance among the other microorganisms inhabiting the subject. We would prefer the treatment to be inexpensive and the dosing schedule uncomplicated. A high dose omeprazole (40 mg thrice daily) plus amoxicillin (750 mg thrice daily) regimen seems ideal except for the high cost of omeprazole and the fact that many patients claim allergy to penicillin.⁸ Standard triple therapy is by far the least expensive. It is

difficult to push the cure rates much below 90%. The disadvantage is that there are a number of different drugs that must be taken and metronidazole resistance may undermine the results. Clarithromycin has the potential to replace metronidazole in any of the metronidazole containing multidrug programmes. Omeprazole, clarithromycin, and metronidazole combinations seem simple, as twice a day dosing, but carry the risk of having the organism develop resistance to both of these extremely important anti-*H pylori* antimicrobial drugs. There is no 'right answer', but there are a number of excellent potential antimicrobial regimens. We recommend that one yielding a cure rate of 90% or greater be chosen and that the drugs be given for two weeks. Our actual approach is to give anti-*H pylori* treatment for two weeks but to continue antisecretory therapy for a total of six weeks.⁹ If we prescribe an omeprazole containing anti-*H pylori* treatment, we generally switch to a less expensive H₂ receptor antagonist during the last four weeks of treatment. Patients are seen at the end of antimicrobial treatment to ascertain whether problems have occurred and to evaluate compliance. They are seen again after four to six weeks to evaluate the effectiveness of treatment using endoscopy or the urea breath test. This general protocol is standardised and thus there is no need to try to remember whether the regimen is of one or two weeks' duration, adequate antisecretory treatment is given to reliably heal the ulcer, the patients continue to take the drugs, and thus (in our practice) are more likely to return for follow up, and it works.

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