Supplemental Material: *H pylori* eradication therapy

The primary reason for treating *H pylori* infections originally was because it is a transmissible infectious disease that universally causes progressive damage to gastro-duodenal structure and function. In addition, the outcome for an individual patient is unpredictable and at least 20% of those infected eventually suffer a clinically important and potentially life threatening disease. The prevalence of the different *H pylori*-related disease outcomes differs geographically. For example, the lifetime risk of gastric cancer is greater than 10% in Japan, Korea, and regions of China [105]. In the US in the 1970's, when *H pylori* was still prevalent in the United States, it was estimated that the lifetime risk of *H pylori*-related peptic ulcer disease was 10% with 25% of peptic ulcer patients experiencing a major life threatening complication. At that time there were an estimated 500,000 new cases of peptic ulcer each year, with more than 400,000 hospitalizations with more than 4,000,000 hospital days devoted to the treatment of peptic ulcer. In addition there were 140,000 operations/year, and 9,000 hospital deaths/year [106]. In the first half of the 20th century gastric cancer was the number one cause of cancer and gastric atrophy was common. Since the late 1980s the discovery of a symptomatic *H pylori* infection has resulted in treatment. This effort and the marked and continuing decrease in *H pylori* prevalence is likely responsible for the inability of a recent epidemiological study using the NHANES III data to show an increase in all cause mortality among those with presumably asymptomatic *H pylori* infections [107]. The most recent focus has been on *H pylori* eradication as a means of eradication of gastric cancer, a major cause of cancer deaths. As noted in the body of the main manuscript, the strategy to accomplish this goal will differ regionally depending on the prevalence and risks in different populations. The United States has been experiencing large number of immigrants from high *H pylori* prevalence areas and high gastric cancer prevalence areas (eg, Asia and Central and South America) such that there are clearly recognizable high risk subpopulations. This is likely manifest as the increase in the rate of distal gastric cancer in Caucasians of both sexes in the 25-39 year old age group reported during the past three decades [108]. Our local experience has been that this group largely consists of immigrants from high cancer incidence regions. The ability to reliably cure *H pylori* infections requires rational use of antimicrobial therapy. Below we discuss how reliable treatment success can be achieved.

Approach to estimation of treatment outcome

Knowledge of the success rate of a particular regimen with susceptible and with resistant infections allows one to estimate the outcome in individuals and in population if the pattern of resistance is known. This is currently true for triple therapies and clarithromycin-containing 3 and 4 drug non-bismuth containing regimes. Data remain insufficient for bismuth quadruple therapy. The basic formula is [the proportion with susceptible strains times the success rate, (eg, 98%) plus the proportion with resistant strains times success rate with resistance. (eg, 10%) [109-110]. One only needs a table showing the cure rates in relation to antimicrobial susceptibility (i.e., all susceptible, resistant to each single antimicrobial and resistant to combinations of antimicrobials) (Table 1 main manuscript).

Examples

7 day Triple therapy: consider a study comparing 7 day triple therapy in a population with no resistance (eg, chosen by antimicrobial testing as a tailored therapy) and the general population which has a clarithromycin resistance rate of 13%. Assume that 7 day triple therapy would be expected to cure approximately 94% of susceptible strains and approximately 10% of those with clarithromycin resistance. In a comparative trial of 200 patients (i.e., 100 with no resistance and 100 from the population) we could have 100 susceptible vs. (87 with susceptible strains and 13 with resistant strains). The simple calculation would be (100 times 94% (considering 94% success rate for susceptible) vs. (94% of 87) plus (10% of 13) = 81.78 + 1.3 = 83%. Thus, the authors would report superiority with 94% vs. 83% ($P<0.001$). However, because the outcome was assured prior to starting the study there could be no valid hypothesis (no clinical equipoise). Such studies continue to be published (eg, [111]).

10 day Sequential therapy: The approach works with complex therapies. For example, for a population with 10% clarithromycin resistance, 30% metronidazole resistance, and 3% dual resistance the equation would be (from Table 1) (# none resistant)(95%) + (# clarithromycin resistant)(80%) + (# metronidazole resistant)(75%) + (# dual resistant) (10%) or (57 X .95) + (10 X .80) + (30 X .75) + (3 X .1) = 54.1 + 8 + 22.5 + 0.3 resulting in 84.9% success pre protocol. The actual result in a clinical trial would likely be somewhat lower because of issues with adherence (i.e., intention to treat result). 14 day sequential therapy would give an improved result.

However, 14 day concomitant therapy would give a much better outcome (i.e., at least 94% per protocol) which is why sequential therapy is now considered obsolete [109-110].

Other drug combinations

This type of calculation is effective for regimens where the success is specifically known in relation in the presence of resistance. Antimicrobials used in triple therapies that become ineffective in the presence of resistance such as fluoroquinolones (eg, levofloxacin), clarithromycin will provided reliably results and one can use the table in references for individual data. There is still insufficient data with regard to hybrid therapy in terms of dual clarithromycin-metronidazole resistance and for convenience one can use the data for concomitant therapy. Bismuth quadruple therapy remains problematic. Overall, the main issue appears to be adherence which effectively reduces the number of days of antibiotic administration [112]. In the few countries where tetracycline resistance or amoxicillin resistance are problems these calculation should be used with caution and data on the effect of these resistances collected. Because countries where a significant proportion of the population are slower proton pump inhibitor (PPI) metabolizers related to CYP2C19 genotypes the results with the dual amoxicillin and PPI component may be more effective and may become important with 14 day therapy approaching 50%. However, this has a minor influence on overall outcome.

What do the results of a clinical trial mean to your patients?

The example with 7 day triple therapy above reported a per protocol result of approximately 83%. This is the result with that specific population. None of their or your patients will achieve 83% as the cure rates were 94% for susceptible and 10% (actually probably closer to 0%) for those with resistant strains. If your patient has received macrolides previously, the odds are they will be in the 0-10% success group. Table 1 below shows the effect of resistance on the outcome of 7 and 14 day clarithromycin triple therapy. The proportion of patients who fail and require retreatment can be estimated as approximately 100 minus the ITT success rate and thus the results in Table 1 are optimistic. In the best scenario treatment success with 7 day triple therapy would fall below 90% (the cut-off for an acceptable therapy) with 5% clarithromycin resistance; 14 day therapy would become unacceptable at 10% resistance. I one knows the resistant pattern in their population, or has a good idea about the pattern in an

individual patient based on history and prior drug use, one can identify which regimens to avoid. It is probably best to ignore all claims of superiority of one regimen over another unless the comparison consisted of regimens that were not equivalent in the presence of the resistance pattern present in the population. Most published results are specific to the population studied and not generalizable. The exception are those based on susceptibility testing.

Suppl. Table 1. Effect of Clarithromycin Resistance on Outcomes (per protocol) of Clarithromycin-containing Triple Therapies*

Resistance	7 day Result	14 day Result
0%	94%	97%
5%	89.8	93.1%
10%	85.6	89.3%
20%	77.2	79.6%
40%	60.4	62.2%
80%	26.8	27.4

*Assumes 10% success with the dual amoxicillin PP component alone