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EDITORIAL

Helicobacter pylori Therapy Demystified

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Abstract

We discuss the role of comparators in *Helicobacter pylori* treatment trials and why anti-*H. pylori* therapeutic trials (an infectious disease) are fundamentally different from common gastrointestinal diseases (e.g., the absence of a placebo response, the expectation that cure rates in excess of 95%, and the ability to understand why treatment fails). No comparator is absolutely required other than to 100% success and comparison trials should be limited to comparisons between therapies that reliably achieve 90% or greater success (i.e., good therapies). Comparisons with known low success regimens (i.e., bad therapies) are unethical as is withholding information from the subject regarding current effectiveness of a regimen even if that information would reduce the likelihood that the subject would volunteer. We also discuss how it is possible to predict the outcome of a published but locally untried new regimen. The reason for different outcomes of typical gastrointestinal therapies is shrouded in mystery. In contrast, treatment success for *H. pylori* should be predictable and treatment failures explainable. For too long expectations and analyses of *H. pylori* therapy has been confused with what is appropriate for gastrointestinal disease such as constipation or irritable bowel syndrome rather than for infectious diseases such as pneumonia.

In this issue of Helicobacter, Calvet et al. [1] present their carefully thought-out views on how to design an *Helicobacter pylori* treatment trial. The authors are among the most experienced in clinical trials of anti-*H. pylori* therapies as well as in the analysis of trials performed by others. They are also remarkably untainted by big PHARMA. The article is highly recommended as a primer for designing therapeutic anti-*H. pylori* trials and should also become a valued reference resource. There are, however, a few caveats.

The authors suffer from a mild case of what we call ''the course of the gastroenterologist'' (also known as ''the compulsion to compare'') [2–4]. This need to compare often arises early in gastroenterology training, and even when unnecessary or inappropriate, the urge appears intractable. The diseases seen by gastroenterologists are usually diseases of unknown cause (e.g., functional, ''autoimmune,'' etc.) and ones that cannot reliably be cured. Most often, we do not fully understand why a particular therapy is effective and we almost never expect our treatment success to approach 100%. Interpretation of studies is further complicated by a considerable placebo response that requires comparisons with placebo to substantiate any claim that the trial actually achieved a positive result [3,4] (Table 1, Fig. 1). Even when the comparator is an active agent, a placebo is often required to ensure that the response to the active comparator was also superior to placebo. Not understanding why a regimen is successful makes it almost impossible to understand why it fails. The degree of response to active drug and placebo often shows variation among trials making meta-analysis a useful tool to assist in identifying differences between therapies and treatment strategies.

Helicobacter pylori infections differ from other problems in gastroenterology primarily because *H. pylori* is actually an infectious disease that was ''captured'' by gastroenterology. *H. pylori* is a common bacterial infections and can be reliably cured using appropriate antimicrobial therapy (i.e., with susceptible organisms, one should expect 100% or near 100% treatment success) [3]. There is also no placebo response, which remarkably changes the requirements for any clinical trial (Table 1, Fig. 2). Failure of a *H. pylori* therapy is

Table 1 Comparison of differences in clinical trials and analyses between typical gastrointestinal diseases and common bacterial infectious diseases

	Disease	
	GI	Infectious
Result predictable	No	Yes
Placebo response	Yes	No
Comparator useful	Yes	No[a]
Meta-analyses useful	Yes	Rarely[a]

[a]Only when comparing highly effective regimens (see text).

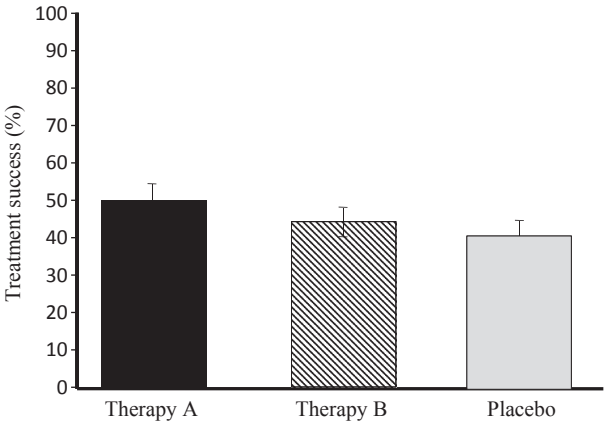

Figure 1 Example of responses to therapy for typical GI disease such as irritable bowel disease, inflammatory bowel disease, constipation where a < 100% success is expected and a placebo is generally needed.

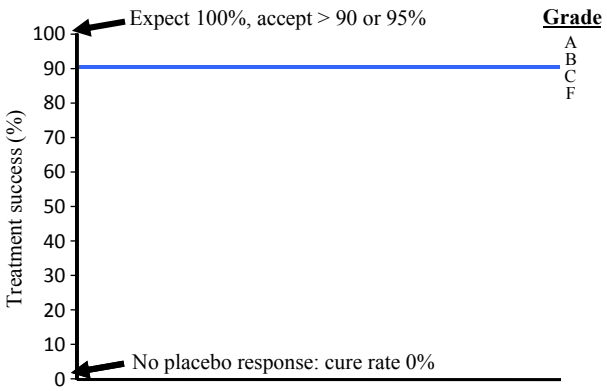

Figure 2 Depiction of the possible outcomes when planning a clinical trial of an anti- *Helicobacter pylori* therapy. The trial should be planned with stopping points if it becomes clear that it cannot achieve the prespecified criteria for a successful trial (e.g., using ordered categories of success) [5].

also almost always explainable in terms of either antimicrobial resistance or a flawed regimen (e.g., in terms of duration, formulation, etc.) (Table 1). Importantly, a regimen that is effective anywhere in the world should be equally effective anywhere else provided that the conditions are the same (pattern of resistance, same drugs and their metabolism). As results of an effective anti-*H. pylori* therapy with susceptible strains should always approach 100% per protocol, one can score the results of a regimen broadly as either good (e.g., reliably provides 90% or greater success, preferably 95% or greater) or bad. Here, we define bad as treatment success of <90% or <85% (if one wishes to include a ''gray'' zone between 85 and 90%).

Table 2 Effect of clarithromycin resistance on outcome of triple therapy

Duration	Regimen cure rate	Range
14 day	PPI-C-A = 95 ± 5%	90–100%
	PPI-A = 30 ± 20%	10–50%[a]
7 day	PPI-C-A = 90 ± 5%	85–95%
	PPI-A = 10 ± 10%	0–20%[a]

[a]Result with clarithromycin-resistant strains.
PPI, proton pump inhibitor; C, clarithromycin; A, amoxicillin.

Normally, as resistance to common bacterial infections (e.g., *Escherichia coli* urinary tract infections, pneumococcal pneumonia, gonorrhea, tuberculosis) increases and success declines to unacceptable levels, new regimens are introduced. Few would consider or recommend comparing the new highly successful regimen with a previous ''locally best'' or ''tradition'' in which resistance had undermined success (i.e., there would be no need to ''prove'' that the new regimen was ''better'' than one that was known to be no longer acceptable locally). However, this seemingly unimaginable scenario occurs often in anti-*H. pylori* clinical trials. Not only are good and bad anti-*H. pylori* therapies compared but also the results are then subjected to meta-analyses, which only prove that what was known to a bad regimen is reliably bad [3]. It is unethical to enter subjects into a trial using a known inferior regimen [2]. It is also unethical to withhold full information from the subject regarding current effectiveness of a regimen even if that information would reduce the likelihood that anyone would volunteer (i.e., an inferior regimen can never be called the ''standard of care'' or ''approved'' in lieu of telling the truth about the actual expected outcome).

If a known bad regimen is not a suitable comparator, what is?

As 100% success can be achieved, 100% success is a comparator of choice with therapies being judged in

terms of how close they come to achieving that level of success. If the best local therapy provides unacceptable low cure rates, it should be abandoned just as was single-drug therapy for tuberculosis or low-dose penicillin for pneumonia or syphilis. We do not suggest that comparisons between regimens should never be performed, rather comparisons should be restricted to known good therapies (i.e., to identify the best in terms of outcome, cost, convenience, side effects, etc.).

Prediction of outcome with published but untried new therapy

One only needs to know the success rates for a *H. pylori* regimen and its components, in relation to the presence of resistance and the level of resistance locally to be able to predict the range of possible outcomes. For example, with legacy triple therapy consisting of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin, the data needed are as follows: the cure rate for the three-drug combination and each of the two dual therapies (i.e., PPI–clarithromycin and PPI–amoxicillin). As amoxicillin resistance is extremely rare, one only needs to know the rates for the triple therapy and the PPI–amoxicillin dual component (Table 2). In the majority of cases, the overall effect is related to the triple component. For example, with 20% clarithromycin resistance, the cure with 14-day triple would be the success with susceptible strains plus the success with clarithromycin-resistant strains. If the success of triple therapy with susceptible strains was 95%, the calculations would be (per 100 subjects) 100 subjects minus 20 failures = 80 susceptible × the cure rate (95%) = 76 cures + the contribution of the dual therapy at 25 or 20 × 25% or four cures for a total treatment success of 80% (from Table 2, the range would be 78 to 86%). For a 7-day therapy, the corresponding results would be a success rate of 74% (range 72 to 76%). The difference between 7- and 14-day therapies is 6%, which also is consistent with data from prior meta-analyses. One can easily calculate the effect of different percentages of clarithromycin resistance (Fig. 3), and it becomes clear that on average, for a 14-day triple therapy, the success rate will fall below 90% when the rate of clarithromycin resistance is approximately 8%.

A similar exercise can be performed for any combination regimen (see reference [3] for examples with sequential, concomitant, and hybrid therapies). The fact that results with different patterns of resistance have rarely been reported makes the calculations with clarithromycin-containing regimens a bit more complicated but is still clinically useful. That is not to say that new regimens should be introduced without testing in a new population but rather one would be able to prospectively predict which regimens will be successful and which should not evaluated because they are destined to fail.

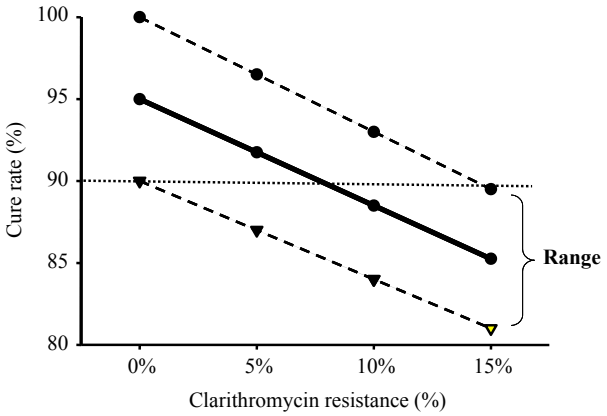

Figure 3 The range of outcomes in relation to the proportion of the population with clarithromycin-resistant infections. The regimen depicted is a cure rate of 95 ± 5% for the three drugs and 30% for the proton pump inhibitor plus amoxicillin dual therapy given for 14 days.

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