Published in final edited form as:

Helicobacter. 2015 October ; 20(5): 321–325. doi:10.1111/hel.12244.

Editorial - Avoiding unethical *Helicobacter pylori* clinical trials: Susceptibility-based studies and probiotics as adjuvants

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Abstract

As a general rule, any clinical study where the result is already known or when the investigator(s) compares an assigned treatment against another assigned treatment known to be ineffective in the study population (e.g. in a population with known clarithromycin resistance) is unethical. Since susceptibility-based therapy will always be superior to empiric therapy in any population with a prevalence of antimicrobial resistance greater than 0%, any trial that randomizes susceptibility-based therapy with empiric therapy would be unethical. The journal **Helicobacter** welcomes susceptibility or culture-guided studies, studies of new therapies and of adjuvants and probiotics. However, the Journal will not accept for review any study we judge to be lacking clinical equipoise or which assign subjects to a treatment known to be ineffective, such as a susceptibility-based clinical trial with an empiric therapy comparator. To assist authors we provide examples and suggestion regarding trial design for comparative studies, for susceptibility-based studies, and for studies testing adjuvants or probiotics.

Introduction

The history of development and use of antibiotics extends back before World War II. Effective therapy of infectious diseases has always been based on providing a sufficient amount of an antibiotic for a sufficient duration to eradicate organisms that were susceptible. When the development of resistance began to reduce the effectiveness of antibiotic therapy, the therapy was changed (eg. giving more drug, providing a second drug to inhibit the mechanism of resistance, modifying the drug, or changing to a new drug)¹. There are now a number of 14-day drug combinations that will reliably cure 95% of *H. pylori* infections (per-protocol) when treating infections with susceptible *H. pylori*. These include 14-day clarithromycin, metronidazole, or levofloxacin triple therapies and concomitant quadruple therapy, sequential therapy and hybrid therapy^{2, 3}. In any given population, none of these regimens are superior to another unless the effectiveness of one of is reduced, for example by the presence of antimicrobial resistance or other factors. For example, in a western patient population with no resistance to metronidazole or clarithromycin, both 14-day

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Potential conflicts: Dr. Graham is also a paid consultant for RedHill Biopharma regarding novel *H. pylori* therapies, for Otsuka Pharmaceuticals regarding diagnostic testing, and for BioGaia regarding use of probiotics for *H. pylori* infections. Dr. Graham has received royalties from Baylor College of Medicine patents covering materials related to ¹³C-urea breath test.

clarithromycin or metronidazole triple therapies would be expected to cure 95% or more (per protocol). However, with a 10% prevalence resistance to clarithromycin and no nitroimidazole resistance, 14-day metronidazole-containing triple therapy then would be expected to have greater efficacy compared with 14-day clarithromycin-containing therapy as the resistant subpopulation would have a marked reduction in cure rate (eg, to 10%) reducing the overall effectiveness in this case from >95% to approximately 88%^{2, 3}.

Theoretically the effectiveness of any therapy can be estimated based on its success with the susceptible strains of *H. pylori* (which contributes substantially to the upper limit) and the success with resistant strains (eg, clarithromycin resistance effectively turns clarithromycin triple therapy into PPI-amoxicillin dual therapy). The results with the two populations (susceptible and resistant) are then used together to estimate the range of eradication proportions in a population^{2, 3}. The proportion of patients who are compliant with the 14-day regimen and achieve successful eradication thus depends primarily on the prevalence of antimicrobial resistance (eg, clarithromycin, nitroimidazole, or fluoroquinolone resistance) in the particular population being treated. As such, if the proportions with susceptible and resistant infections are unknown, the results with any population cannot be generalized to another population with a different proportion of antimicrobial resistance. It follows that studies that simply publish the proportion cured without relating the results to the prevalence of resistance in that population are population-specific and not generalizable outside the particular population treated.

Short primer of clinical equipoise

One of the critical elements that defines whether a clinical trial is ethical is the presence of clinical equipoise which is defined as a genuine uncertainty regarding the effectiveness of one treatment compared to another in that particular population⁴⁻⁷. Research subjects should never be exposed to the risks of valueless research (i.e. the answer is already known or the question is trivial), nor should they knowingly be assigned (randomly or otherwise) to a known inferior treatment^{2, 5, 6, 8}. By definition, a comparative trial is unethical if it includes a therapy known (at the time) to be inferior. An ethical clinical trial also requires that the investigator critically analyze the information currently available, and attempt to discover information before and during the trial, that would be relevant to the subject's decision to participate. This information cannot be withheld and must be included in the consent form, provided to the relevant institutional review boards and to the subjects on therapy^{2, 4}. The study should also have a sufficient sample size to establish a difference in efficacy or effectiveness, if one truly exists.

Ethical vs. unethical questions

Unethical questions in the presence of condition C

For example, investigators know that regimen A and regimen B provide excellent results in populations with all susceptible infections or with minimal levels of resistance (eg, <5%). Condition C (eg, clarithromycin resistance) reduces the effectiveness of A but not B. Therefore, when condition C is present, B will always be more effective than A and any

assignment (eg. randomized assignment) of A vs. B done where condition C is known to be present would therefore be unethical.

How to determine the effectiveness of treatments A or B in the presence of condition C? This information has originally come from clinical trials where a new regimen was given to a patient population (eg, the original clarithromycin triple therapy study) and samples for culture were obtained prior to the study and the results analyzed afterward. This provided direct information regarding the effectiveness in the presence or absence of resistance. If one wished to examine the effectiveness of a new combination therapy in the presence of resistance, one could test the new regimen stratified by antimicrobial resistance status (in subjects known to be resistant to one component and in subjects known to be susceptible to one component such as to clarithromycin). Such a study should include appropriate stopping rules and truly informed consent. However, studies comparing the efficacy of assigned (eg. randomly assigned) treatments where one treatment is known to be superior to the other in the presence of antimicrobial resistance are not ethical. As noted previously, studies of antimicrobial therapies without provisions for susceptibility testing are generalizable only to that specific population. There are many examples of large studies where the lack of susceptibility-based results resulted in misleading conclusions and inappropriate generalizations⁹ which then led to subsequent studies in which patients obtained poor results¹⁰. There are also examples where information available prior to the study regarding treatment efficacy (eg. that a short duration of therapy <7 days will not be effective) and susceptibility data were not taken into account, and where susceptibility testing was not done, and despite large sample sizes and ample available budgetary resources, the results failed to identify any clinically useful therapies for the populations involved¹¹.

Susceptibility-based therapy

Susceptibility-based therapy, whether using culture or molecular tests to determine the presence of antimicrobial susceptibility, allows one to select a regimen exclusively containing antibiotics to which the patient's *H. pylori* infection is susceptible. By definition, the prevalence of resistance will be 0% when using susceptibility-based therapy. Susceptibility-based therapy using conventional methods or molecular methods will always yield a higher eradication proportion when compared with an empiric therapy in any given population that contains any resistant strains. Therefore, clinical trials which assign some patients to empiric therapy and others to susceptibility-based therapy lack clinical equipoise and are, by definition, unethical.

Molecular or culture-based susceptibility

The validity of molecular-based susceptibility testing should be assessed by comparing them to the current gold standard traditional methods in the same patients. Potentially, molecular-based methods could technically be superior to the gold standard as they theoretically are a better method to identify the presence of mixed resistance and thus possibly better define the susceptible populations. Treatment outcome would be the clinical arbiter of whether superior identification of mixed resistant and susceptible populations was clinically important. Cost-

effective studies could also be of use to define the threshold level of resistance when susceptibility testing becomes cost effective.

Can one do ethical studies with adjuvants or probiotics?

Clinical trials and meta-analyses have shown that probiotics alone or the addition of probiotics to traditional therapies have generally provided small or no improvements to treatment efficacy and no or only a slight reduction in side effects^{2, 12–15}. The typical study which aimed to measure efficacy has involved populations where resistance had reduced the efficacy of standard therapy to an unacceptable level. The study design often involved randomization of subjects to receive the known suboptimal *H. pylori* therapy plus a probiotic or that therapy plus a matching placebo. Conducting this type of trial where subjects are assigned to treatments in which one or all treatment arms are known with a fairly high level of certainty to lack efficacy (based on the existing body of evidence from a variety of relevant populations) are not ethical.

It is however possible to address ethically the question of whether the addition of a probiotic or adjuvant will enhance treatment effectiveness. To do so requires avoiding comparison with a known ineffective therapy. For example, one could test whether probiotics could reduce adverse events or improve compliance with an effective therapy and thus in that subgroup also improve efficacy. For example, one could randomize subjects to an effective therapy whose success is often compromised by a high frequency of adverse events to a probiotic or placebo. One difficulty with the analysis of such a study is that there appears to be a strong placebo effect among *H. pylori* infected populations (many of whom are included in trials with symptoms at baseline consistent with the adverse events they experience during treatment)¹⁶.

The difficulty arises in attempting to test whether a probiotic or adjuvant could improve treatment efficacy when the efficacy of a standard of care regimen has been lowered by antimicrobial resistance or other factors. To do so would require full disclosure (i.e., that all would be receiving a regimen that would produce many treatment failures) and few subjects would likely volunteer and many institutional review boards would deem the study to be unethical. While most published studies have used this approach and some reported some improvement in treatment success none has resulted in cure rates >90%. Importantly, the study design also precluded the authors from measuring the actual degree of improvement among participants. Subjects receiving clarithromycin triple therapy consist of two subgroups: one with susceptible strains that will achieve high cure rates despite the probiotic co-therapy and a group with clarithromycin resistant strains that effectively receives only PPI-amoxicillin dual therapy and is expected to achieve a lower proportion of cures. The results reported from the available studies represent the average of the two subgroups. The effectiveness of dual PPI-amoxicillin therapy in the subgroup with clarithromycin resistance is strongly influenced by the dose and type of PPI used, the proportion with CPY2C19 polymorphisms that enhance PPI effectiveness, and the proportion of subjects with pretreatment hypochlorhydria. The average results cannot be attributed to each subpopulation (they are uninterpretable) and also cannot be used for any other population.

One potential approach to address the question about the possible efficacy benefit from the probiotic/adjuvant is for the experiment to be done as a proof of concept pilot study in volunteers. Since the majority of benefit would accrue to those with clarithromycin resistant strains, the experiment could be restricted to the dual PPI-amoxicillin therapy. The subjects would be fully informed volunteers. The design would likely require a predefined target defining acceptable success (e.g., minimum cure rate of 70%) and employ study termination rules to limit the exposure in the event that it became clear that “success” could not be achieved^{17, 18}. The initial studies could likely be restricted to the dual therapy plus probiotic/adjuvant arm.

Summary

As a general rule, any clinical study where the result is already known or when the investigator(s) compares an assigned treatment against another assigned treatment known to be ineffective in the study population (e.g. in a population with known clarithromycin resistance) is unethical. Since susceptibility-based therapy will always be superior to empiric therapy in any population with a prevalence of antimicrobial resistance greater than 0%, any trial that randomizes susceptibility-based therapy with empiric therapy would be unethical. A number of such trials^{19–28} and reviews^{29, 30} have been published and others are currently in review. Most high impact journals no longer accept comparative trials where the comparator is known to be inferior. The journal **Helicobacter** welcomes susceptibility or culture-guided studies, studies of new therapies and of adjuvants and probiotics. However, the Journal will not accept for review any study we judge to be lacking clinical equipoise or which assign subjects to a treatment known to be ineffective, such as a susceptibility-based clinical trial with an empiric therapy comparator.

Acknowledgments

Support: Dr. Graham is supported in part by the Office of Research and Development Medical Research Service Department of Veterans Affairs, Public Health Service grants DK067366 and DK56338 which funds the Texas Medical Center Digestive Diseases Center. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the VA or NIH.

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