Helicobacter pylori: Therapeutic Targets

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Helicobacter pylori is now considered a major pathogen of the upper gastrointestinal tract. It is seen as an important cause of peptic ulceration not associated with NSAID use. It is also increasingly linked to other diseases of the GI tract, although the relationship between the organism and conditions such as gastric cancer, non-ulcer dyspepsia and gastroesophageal reflux disease is not as clear as is the case in peptic ulcer disease. This is probably because of a lack of well-performed, statistically powerful, prospective therapeutic trials that indicate that H. pylori eradication is of benefit in these diseases. The high infection rate without overt disease seen in many populations, especially from developing countries, probably contributes to this "credibility gap."

While we have excellent therapeutic regimens available at this time, rational targeting requires that the objective evidence in favor of therapeutic intervention in upper GI disease, as well as the local H. pylori epidemiology, needs to be considered.

INTRODUCTION

Helicobacter pylori was re-introduced to a skeptical gastroenterological community in 1983. It is of interest to note that even the landmark letters to the Lancet were of different styles: Goodwin records that clinician and histopathologist could not agree on the wording of a common letter [1]. In his letter, Warren described the histological findings associated with the unidentified curved bacilli found in active chronic gastritis [2]. Marshall, on the other hand, did not limit himself to describing abnormalities; he extrapolated the findings noted, linking them to what was known regarding the association between gastritis and associated diseases "i.e., peptic ulcer and gastric cancer" [3]. These original communications appear to have set the scene for the thought processes with regard to H. pylori in the gastroenterological community. On the one hand, a cautious, evidence-based approach, and on the other, a more intuitive approach, which may be a bit cavalier for many. This dichotomous approach is also evident when targets for H. pylori therapy have been defined.

THE NEED FOR TARGETING H. PYLORI THERAPY

There clearly is a need for defining therapeutic targets for H. pylori. Three surveys have reported on the approach of gastroenterologists and general practitioners to H. pylori, dyspepsia and upper gastrointestinal disease. Milne et al. [4] reported that 73 percent of 670 members of the British Society of Gastroenterology thought that H. pylori was a cause of duodenal ulcer, but that only 25 percent used H. pylori eradication therapy in duodenal ulcer disease at first presentation. More surprisingly, although 75 percent of

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\*Abbreviations: PPI, proton pump inhibitor; EHPSG, European Helicobacter pylori study group; GERD, gastroesophageal reflux disease.
respondents did not agree that \textit{H. pylori} was a cause of non-ulcer dyspepsia, 69 percent used anti-\textit{H. pylori} therapy to treat patients with this condition.

The situation in general practice appears to be no less confused. Penston and Mistry [5] report that of the 154 patients treated for \textit{H. pylori} who they studied, \textit{H. pylori} status was known in only one-third of patients before treatment and in only 15 percent after treatment. In addition, 56 different treatment regimens were used to treat these 154 patients. Not surprisingly, the outcome of treatment was disappointing. Bodger et al. [6] record a similar confusion in prescribing patterns, with a wide variety of diagnoses being treated for \textit{H. pylori}.

**TARGETING \textit{H. pylori} THERAPY**

If a condition that is thought to be related to \textit{H. pylori} infection is to be specifically identified as a therapeutic target, the following information pertaining to both \textit{H. pylori} and the condition is needed:

1. Can the infection be cured?
2. Is cure of the infection permanent or transient?
3. What is the long-term outcome of the infection and, related to this, what is the outcome of intervention?

\textit{Can the infection be cured?}

\textit{H. pylori} therapy has evolved from complicated, high-frequency therapy with a high side-effect rate ("Triple Therapy"), through a flirtation with proton pump inhibitor (PPI)\textsuperscript{\textcopyright} dual therapy (safe, simple, but not universally effective) to the current PPI-based triple therapy. The latter has come closest to satisfying the criteria for an "ideal" anti-\textit{H. pylori} therapy: the regimens are simple, generally well tolerated, with eradication rates generally exceeding 80 percent on an intent-to-treat basis. Further development of these PPI-based triples is still needed: local resistance profiles have to be elucidated, and the optimal duration of co-therapy (i.e., seven or ten days, or perhaps even less than seven days) still has to be determined. Despite these considerations, clinicians currently have effective therapy available, which, although expensive, is likely to be cost effective in conditions where the natural history of the disease is effectively changed. The proviso, of course, is that prescribing habits will change and that physician visits will be reduced following therapy.

\textit{Is cure of \textit{H. pylori} permanent or transient?}

Available information suggests that, once effectively treated, cure is permanent in developed countries, with re-infection rates lower than 1.5 percent [7]. The situation in developing countries is less well studied. Initial observations suggested re-infection rates on the order of 20 percent per annum in this setting [8], but more recent observations suggest a lower annual re-infection rate, of the order of five percent per annum [9,10]. Studies are, however, small and more data are needed before firm conclusions can be drawn regarding the permanency of cure in the high prevalence setting of the developing world.

\textit{What is the long-term outcome of \textit{H. pylori} infection and therapeutic intervention?}

\textit{H. pylori} infection of the stomach is always associated with gastritis, and \textit{H. pylori} has been shown to cause gastritis, fulfilling Koch's postulates [11]. The major conceptual
problem, however, is that the vast majority of subjects infected with the organism will not go on to develop any of the specific upper gastrointestinal disease syndromes postulated to be caused or associated by infection with *H. pylori* (peptic ulcer disease, gastric carcinoma, MALT-lymphoma), and the factors determining which subjects will progress from simple gastritis to a specific disease state are not well defined at present. The relationship of *H. pylori* with other major upper gastrointestinal disease syndromes (non-ulcer dyspepsia, gastroesophageal reflux disease (GERD)) is, at best, speculative.

A major stumbling block to accepting a dominant role for *H. pylori* in the etiology of the major upper gastrointestinal disease relates to the inability to reconcile the high infection rate, especially in developing countries, with the low disease rates reported from these countries—in short, the “African enigma.” Given the inability to prove a causal relationship between *H. pylori* infection and specific diseases, a lot of emphasis has had to be placed on the association between infection and disease as well as the effect of therapeutic intervention, two of the criteria Hill suggested to determine the relationship between an environmental agent and disease [12].

At this stage, the only disease state in which *H. pylori* eradication has proven unequivocally to be beneficial is peptic ulcer disease, not associated with NSAID use [13]. This benefit appears to be universal [9, 10], sustained [14] and applicable to peptic ulceration complicated by bleeding [15].

A host of contentious issues remain. Using analytical epidemiological tools, gastric carcinoma has been linked to *H. pylori* infection, the organism being classified as a Group I carcinogen [16]. Non-ulcer dyspepsia is a popular therapeutic target, although the evidence in favor of an etiological role for *H. pylori* is based on poorly designed, inadequately sized studies [17, 18]. More recently, GERD, the one condition of the upper gastrointestinal tract previously thought to be in no way related to infection with *H. pylori*, has become a therapeutic target as a result of a single study suggesting accelerated progression of fundal gastritis in *H. pylori*-positive subjects treated with PPIs [19]. This targeting, while conceptually appealing because of the historical observations relating to the migration of *H. pylori* during PPI therapy, is based on an inherently flawed study, using as it does two apparently different populations as study subjects and controls.

**ATTEMPTS AT THERAPEUTIC TARGETING FOR *H. PYLORI***

There have been two attempts at targeting therapy for *H. pylori*. The first, a consensus statement by the National Institutes of Health in 1994 [20], followed the conservative, evidence-based approach in their recommendations. Based on available evidence, the NIH guidelines, as they became known, recommended treatment for *H. pylori* only in subjects with documented *H. pylori* infection and non-NSAID associated peptic ulcer disease. These guidelines confirmed those of four years earlier, made to the World Congress of Gastroenterology [21]. The guidelines have two important virtues: they are rugged and have stood the test of time, while the recommendations can be universally applied. Specifically, they are as appropriate in the developed world as they are in the developing world.

It was soon apparent, however, that the “real world” indications for *H. pylori* therapy were being broadened. The European Helicobacter Pylori Study Group (EHPSG) has recently suggested guidelines for the management of *H. pylori* infection [22]. The EHPSG combined an evidence-based approach with a consensus-based approach in evaluating evidence and making their recommendations. The following resulted: *H. pylori* eradication was strongly recommended in all infected peptic ulcer patients, bleeding peptic ulceration, low-grade MALT lymphoma, gastritis with severe macro- or microscopic
abnormalities and following resection of early gastric cancer. Eradication was further considered advisable after appropriate investigation in patients with non-ulcer dyspepsia, those with a family history of gastric cancer, before long-term PPI therapy in GERD, when NSAID therapy is planned or ongoing, following gastric surgery for peptic ulcer disease or gastric cancer and in response to the patient's wishes. The EHPSG were certain as to whether eradication should be advised in H. pylori-positive asymptomatic subjects and in those with extra-alimentary disease. The EHPSG suggested, furthermore, that it is acceptable for dyspeptic patients, younger than 45 years and without "alarm" findings, who test positive for H. pylori, to be treated for the infection without further investigation at initial presentation.

The EHPSG guidelines represent an important departure from the evidence-based guidelines of the past and can essentially be seen as an attempt to endorse the "real world" practice. The guidelines have, however, lost their universality. It would be difficult to apply these guidelines in areas of high gastric cancer prevalence, while the high prevalence of the infection (and the low prevalence of disease) in developing countries makes the testing of dyspeptic subjects an unproductive waste of resources.

**CONCLUSION**

We have come a long way since the isolation of H. pylori in 1983. Effective therapy for H. pylori has been developed, and there is still better to come. Peptic ulcer disease has become medically curable. We are starting to unravel the relationship between the organism and the causation of disease.

The only unequivocally proven target disease for the eradication of H. pylori remains H. pylori-associated, non-NSAID driven, peptic ulcer disease. Broader “guidelines” should be interpreted with care and in the practitioner’s local context.

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