The future of *Helicobacter pylori* infection

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Helicobacter pylori was first isolated more than two decades ago. Despite the fact that this achievement was acknowledged by awarding of the Nobel prize, the thinking about what is the proper medical response to *H. pylori* had continued to evolve. Initially, *H. pylori* infection was seen largely in the context of duodenal ulcer disease. In fact, even today the U.S. Food and Drug Administration (FDA) only accepts treatment of ulcer disease as a indication for therapy *H. pylori*.

Effects of the initial discovery

Acceptance of *H. pylori* as a pathogen and not a colonizer of inflamed gastric mucosa appeared to be slow. Possibly, one problem was that the discovery was presented as if were entirely new as there had been long interest in a possible infectious cause of gastritis and ulcer disease. In the 1970s extending through the period of its initial culture, Steer and colleagues in the U.K. had been studying and attempting to culture the spiral-shaped bacteria associated with gastritis.[1-3] One might wonder if acceptance of the concept would have been surrounded by less controversy if the discovery had been introduced as a major advance in solving an old problem. Despite the presence of associations of the organism with gastritis and with peptic ulcer, physicians required proof that eradication of the infection would result in cure of peptic ulcers. Achieving this goal was not easy

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as it required the ability to easily and reliably diagnose the infection as well as effective therapies.

H. pylori was introduced in the early 1980s which was an era of exciting progress in Gastroenterology related to the discovery and clinical introduction of the first truly specific anti-secretory drugs (H_2-receptor antagonists and proton pump inhibitors) and of increasingly useful fiberoptic endoscopes. Acid-related ulcer disease had come to dominate both research and practice in gastroenterology such that investigators, opinion leaders, and pharmaceutical companies were already convinced that they had effective ulcer therapy available (ie, why should they abandon all that was new for what an unproven concept that appeared to come out of the blue? Gastroenterology therefore was unwilling to abandon 50 years of research and clinical advances but rather continued what was effective proven effective therapy until the data became available that changing would benefit the patients (ie, be superior to what they were doing).

Warren and Marshall's discovery was not ignored; many investigators immediately began studies to investigate this new organism and its possible role in disease. Considering how much there was to do, change actually came quite rapidly as new diagnostic tests were developed and different therapies were tested. By the early 1990s sufficient data had accumulated to show that *H. pylori* eradication would change the natural history of peptic ulcers such that "no acid – no ulcer" "became "no *H. pylori* – no ulcer". This paradigm shift marked the beginning of the realization that peptic ulcer disease was a gastrointestinal manifestation of an infectious disease. However *H. pylori* remained closely associated with ulcers and was largely remained a gastrointestinal problem rather than an infectious disease problem.

H. pylori **as an infectious disease that causes gastritis**

H. pylori should primarily be thought of as a cause of gastritis. Gastritis had long been known to be tightly associated with pernicious anemia, iron deficiency anemia, peptic ulcer disease, and gastric cancer. In 1938 Konjetzny wrote: *"Ulcer and gastric cancer will be developed through silent inflammation of gastric mucosa. We are not able to distinguish between gastritis, which forms benign ulcer and that developing gastric cancer. When we were able to prevent gastritis or treat it, we would be able to prevent ulcer and gastric cancer: Prophylaxis of gastritis means prophylaxis against ulcer and gastric cancer".*[4] In their first report, Marshall also speculated that eradication of the organism would also eliminate both peptic ulcers and gastric cancer.

In some regions of the world peptic ulcer remains a major problem. In others, gastric cancer is a major killer. Both are direct outcomes of *H. pylori* gastritis but they reflect different patterns of gastritis which in turn is related to the different environmental factors that interact with bacterial and host factors. The tendency to focus on the peptic ulcer or

gastric cancer led investigators away from why the patterns of gastritis differed resulting in many investigators to journey down relatively unproductive paths.

H. pylori and gastric cancer

Sufficient data are now available for one to unconditionally state: no *H. pylori* no gastric cancer. Eradication of *H. pylori* after the precursor lesion (atrophic gastritis) has developed will reduce but not eliminate cancer risk. Eradication before atrophy occurs will essentially entirely prevent gastric cancer. The recent studies from Japan where *H. pylori* eradication reduced the development of metachronous cancers among patients at the highest risk (ie, those who had already developed gastric cancer) showed that elimination of the infection even in the highest risk group was beneficial.[5] Within the next few years, countrywide *H. pylori* eradication programs will begin in Japan and this will rapidly spread to Korea and China. No one deserves, needs or benefits form a *H. pylori* infection. As the lay population learns this truth, they will increasingly demand that *H. pylori* be eradicated from their country also.

Impediments to worldwide *H. pylori* eradiation

The two major impediments are A) that *H. pylori* needs to be considered an infectious disease like any other infectious disease and B) in underdeveloped countries, the recurrence rate after *H. pylori* eradication is high making permanent eradication difficult if not impossible.

H. pylori as an infectious disease

The expectations regarding cure rates with a typical infectious disease is that a course of therapy will cure the infection in almost 100% of cases. When resistance arises and an antibiotic no longer provides near 100% cure rates, it is no longer used if others are available that will provide the expected high success rate. In most infectious diseases, physicians are continually updated with regard to the patterns of antibiotic resistance to important pathogens they see. They can also judge whether the therapy is successful by following the course of the illness in the patient. In contrast, most *H. pylori* treatments are empiric and follow-up testing is often not done such that physicians remain ignorant of whether they generally succeed or fail. Many talks and the majority of consensus statements regarding *H. pylori* therapy are heavily influenced by "opinion leaders" defined as physicians who directly or indirectly are rewarded by Pharma. It is impossible to imagine a clinical trial of a typical infectious disease (eg, a urinary tract infection) where a new highly successful therapy would be compared to an older drug which had increasing failed because of increasing resistance. Yet, this is the standard for *H. pylori* therapy. There are also ethical

considerations in that study patients must received informed consent (ie, be told what the physician knows and expects regarding outcome with the different regimens).

In other infections, success is judged by the proportion cured and if the success rate is below 95% the therapy is generally considered inferior and to be avoided if other better therapies are available. We proposed that the same standards be used for *H. pylori* (ie, that we abandon the "better than" approach and use an "achieved a pre-specified result" outcome measure.[6-8] *H. pylori* is an infectious disease and should be considered as such. This alone will prevent thousands of patients from continuing to receive inadequate therapy (eg, current triple therapy). I predict this change is soon in coming and, after it occurs, we will look back on where we came from and wonder why we made such decisions.

High recurrence rates in developing countries

The problem of unsanitary environments, poor standards of living, and unsafe drinking water will not be solved easily. These same countries have a high prevalence of *H. pylori* infection and often, if not generally, have high reinfection rates after successful eradication therapy. Although it is possible that one could eliminate or reduce this problem by simultaneously treating most or all of the population, that option is unlikely to be attempted. The solution to the *H. pylori* problem in large portions of the world is likely to depend on the development of a successful vaccination strategy. The infection will become increasing important as Japan, Korea and China initiate country wide *H. pylori* eradications programs. Proof of principle has been obtained by successful vaccination of animal models. I predict that the problem will also be solved in humans with will hasten the complete eradication of *H. pylori* worldwide.

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