**Helicobacter pylori Update: Gastric Cancer, Reliable Therapy, and Possible Benefits**

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*Helicobacter pylori* infection contributes to the development of diverse gastric and extragastric diseases. The infection is necessary but not sufficient for the development of gastric adenocarcinoma. Its eradication would eliminate a major worldwide cause of cancer death, therefore there is much interest in identifying how, if, and when this can be accomplished. There are several mechanisms by which *H pylori* contributes to the development of gastric cancer. Gastric adenocarcinoma is one of many cancers associated with inflammation, which is induced by *H pylori* infection, yet the bacteria also cause genetic and epigenetic changes that lead to genetic instability in gastric epithelial cells. *H pylori* eradication reduces both. However, many factors must be considered in determining whether treating this bacterial infection will prevent cancer or only reduce its risk—these must be considered in designing reliable and effective eradication therapies. Furthermore, *H pylori* infection has been proposed to provide some benefits, such as reducing the risks of obesity or childhood asthma. When tested, these hypotheses have not been confirmed and are therefore most likely false.

**Keywords:** Bacteria; Stomach Cancer; Prevention; Barrett’s Esophagus; Esophageal Adenocarcinoma.

*Helicobacter pylori* infection is related etiologically to gastric cancer. For reviews of basic issues related to the ability of *H pylori* to survive on the surface of the stomach, the role of virulence factors in the pathogenesis of gastric cancer, *H pylori*-induced inflammation and genetic instability in the gastric mucosa, and on the history of *H pylori*-related disease, see articles by Salama et al., Yamaoka and Graham, Hanada and Graham, Hardbower et al., Graham, and Shiotani et al. Elimination of *H pylori* will reduce the incidence of gastric cancer dramatically. However, it is not clear how to reliably cure the infection or whether there might be populations in which *H pylori* might provide some benefit. There are several animal models of *H pylori*-induced carcinogenesis, but unless the bacteria are combined with a chemical carcinogen, none of these models reliably produce a malignancy similar to that observed in human beings. More importantly, curing the infection in animal models frequently results in resolution of the malignancy or dysplastic changes, calling into question their relevance to human gastric adenocarcinoma. We review the effects of *H pylori* infection and challenges to and benefits of its eradication.

**H pylori as the Primary Cause of Gastric Cancer**

*H pylori* infection is necessary but not sufficient for the development of *H pylori*-associated gastric cancer, similar in concept to hepatitis B and C viruses and the human papilloma virus. The infection is required for gastric cancer to develop, but *H pylori* infection alone is not sufficient for gastric carcinogenesis—other events also are involved. However, *H pylori* is not the only cause of gastric cancer—other less common causes account for 3%–5% of gastric adenocarcinomas and include infection with the Epstein–Barr virus, genetic abnormalities in the host, autoimmune gastritis, and possibly proximal cancers related to esophageal adenocarcinoma. Therefore, even in the absence of *H pylori*, gastric adenocarcinoma would almost, but not completely, disappear.

Gastric cancer is a major cause of cancer death worldwide. Japan has a particularly high burden of gastric cancer, so in February 2013 the Japanese government approved insurance coverage for a gastric cancer prevention program that includes *H pylori* screening and treatment (primary prevention), as well as post-treatment surveillance (secondary prevention for people with atrophic gastritis). In November 2014 the World Health Organization published an IARC working group report entitled, “*H pylori* eradication as a strategy for preventing gastric cancer,” this report resulted from a conference held in December 2013. In addition, recommendations of the Kyoto Global Consensus Conference on *Helicobacter pylori* gastritis (held in January 2014) were published in early 2015. Those recommendations state: “*H pylori* gastritis should be defined as an infectious disease, even when patients have no symptoms and irrespective of complications such as peptic ulcers and gastric cancer…*H pylori*-infected individuals should be offered eradication therapy, unless there are competing considerations,” and “eradication of *H pylori* reduces the risk of gastric cancer. The
degree of risk reduction depends on the presence, severity, and extent of atrophic damage at the time of eradication.\textsuperscript{15}

Overall, it appears the tide has turned toward \textit{H. pylori} eradication and the question of whether it can eliminate gastric cancer has become moot—similar to asking whether eradication of polio virus infections would eradicate polio. The current issue is how to eradicate \textit{H. pylori} in the most efficient and cost-effective manner. For example, should the entire population of Japan be treated for infection? Should high-risk and high-prevalence groups in regions of low gastric cancer incidence, such as the United States, be treated? The magnitude of the problem is illustrated by the fact that Japan and Korea alone, each with a high prevalence of gastric cancer, have approximately 80 million \textit{H. pylori}-infected individuals. Although \textit{H. pylori} eradication may be possible in Japan and Korea, eradication in other countries with many infected people, such as India, is probably unlikely owing to costs, the presence of other important infectious diseases, and the immense number of people who would require treatment. In addition, in India and other developing countries, there is a high risk for re-infection because of poor sanitation and low standards of living. Vaccination is a possibility, but progress toward a preventive, or preventive and therapeutic, vaccine has been disappointing and funding for vaccine research is scarce.\textsuperscript{15} To date, in the 21st century we have greatly increased our understanding of the pathogenesis of \textit{H. pylori}-related diseases and mucosal immunology, therefore many problems of \textit{H. pylori} vaccine development no longer seem insurmountable.

\textbf{\textit{H. pylori}–Associated Gastric Cancer}

Atrophic gastritis, the precursor to gastric cancer, leads to little or no secretion of acid, which alters the gastric microbiome.\textsuperscript{5} The outcome of each individual infection is unpredictable, as is the rate of progression of the gastric mucosal damage. However, further progression is stopped by eradication. Eradicating \textit{H. pylori} before the development of atrophic changes essentially can eliminate cancer risk. Depending on the degree and extent of atrophic changes, eradication can stop and possibly partially reverse the changes that occurred with atrophy and thus reduce the associated cancer risk. As such, there is a point in the progression of the disease when a significant risk of cancer development remains despite \textit{H. pylori} eradication. It is at this point that secondary prevention (eg, endoscopic surveillance) programs may become cost effective in reducing gastric cancer deaths.\textsuperscript{5,17,18} Candidates who might be suitable for noninvasive, secondary prevention surveillance programs can be identified based on serum levels of pepsinogen, which can be used to determine their risk for gastric cancer (Figure 1).\textsuperscript{5,15,19,20} Such an approach obviates the need for endoscopy for most subjects; patients potentially at risk then can be identified specifically using validated histologic staging systems such as the Operative Link on Gastritis Assessment (OLGA) stages.\textsuperscript{15} Importantly, assays that measure serum levels of pepsinogen cannot identify patients with gastritis accurately if they are receiving proton pump inhibitors or after \textit{H. pylori} eradication.\textsuperscript{6,21,22}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Screening and follow-up approaches. The approach is based on initially identifying patients with \textit{H. pylori} infections and assessing the health of the gastric mucosa using noninvasive testing with a locally or regionally validated IgG \textit{H. pylori} serology and serum pepsinogen tests. Patients without \textit{H. pylori} infection or atrophic gastritis would require no further evaluation or follow-up evaluation. All patients with \textit{H. pylori} infections would undergo eradication therapy; eradication should be confirmed using noninvasive tests such as the urea breath or stool antigen assays. After \textit{H. pylori} eradication, patients with nonatrophic gastritis would require no further follow-up evaluation. Patients with suspected atrophic gastritis (based on their pepsinogen level) would undergo endoscopy for further risk stratification by a validated histologic staging system. Patients cured of \textit{H. pylori} infection and healed nonatrophic gastritis would require no further follow-up evaluation. Patients with confirmed atrophic gastritis (eg, Operative Link on Gastritis Assessment [OLGA] stages III or IV) would be considered for a long-term endoscopic surveillance program. Because their cancer risk is likely to decrease with time, these patients also might be included in studies of surveillance intervals or to determine whether anti-inflammatory or anti-oxidant adjuvant therapies could reduce the risk further. There are not enough data available to make recommendations for patients who have undergone \textit{H. pylori} eradication therapy but who still have mild atrophy (eg, OLGA I and II stages). Further studies are needed to determine the best management strategies for these individuals.}
\end{figure}

The ability of \textit{H. pylori} eradication to prevent gastric carcinogenesis depends on a patient's level of cancer risk at the time that \textit{H. pylori} is eradicated. Patients with nonatrophic gastritis can expect complete or nearly complete protection. Those with irreversible changes to the gastric mucosa have a significant risk, but can be assured that their risk will not increase and likely will decrease. Risk stratification also allows for identification of patients who might benefit from a post-\textit{H. pylori} eradication secondary cancer prevention program. The benefits of \textit{H. pylori} eradication also extend to those at highest risk for cancer death, such as patients who have early gastric cancer (gastric
adenocarcinoma confined to the mucosa and submucosa of the stomach, with or without regional lymph node metastases). Among patients who have had successful endoscopic removal of an early gastric tumor but remain infected with *H pylori*, the risk of metachronous gastric cancer ranges from 1% to more than 4% per year. *H pylori* eradication reduces that risk by approximately 3-fold.23,24

The evidence that *H pylori* eradication reduces gastric cancer risk has led to questions of what *H pylori* eradication accomplishes and how to best use this knowledge. *H pylori* contributes to gastric carcinogenesis by producing persistent acute-on-chronic inflammation and genetic and epigenetic changes that contribute to genetic instability in the gastric epithelium. During tumor progression, gastric cancer cells acquire the ability to evade immune destruction, suppress the immune response, and begin to invade surrounding tissues.3,6,25 Interactions between *H pylori* and other members of the gastric microbiome, endogenous factors, and exogenous factors also can produce carcinogens within the stomach.6 Environmental factors, especially diet, are important determinants of risk for populations (ie, different diets or methods of food preservation can affect the severity of *H pylori*-induced gastric mucosal damage and cancer risk).5,26

*H pylori*-induced inflammation leads to high gastric endothelial cell turnover and a microenvironment that is high in reactive oxygen and nitrogen species, increasing opportunities for DNA damage and somatic mutations3,27–29 (Figure 2). *H pylori* can induce methylation of multiple CpG islands, especially at sites encoding tumor suppressors such

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**Figure 2.** Interactions among inflammation, bacteria, and the epithelium leading to gastric cancer. We show the interaction of *H pylori*, environmental factors, and inflammation in the pathogenesis of gastric cancer. Each plays important roles leading to progressive chromosome instability. *H pylori*-induced inflammation leads to high gastric endothelial cell turnover and a microenvironment that is high in reactive oxygen and nitrogen species, increasing opportunities for DNA damage and somatic mutations. IL, interleukin; ROS, reactive oxygen species. Adapted from Hanada and Graham3 and Chang et al.28
as E-cadherin.\textsuperscript{30} \textit{H pylori} also stimulates activation-induced cytidine deaminase, which alters nucleotides.\textsuperscript{31–33} Furthermore, \textit{H pylori} infection can lead to double-stranded breaks in DNA and alter expression of microRNAs to increase genetic instability.\textsuperscript{3,6} Many, if not most, of these \textit{H pylori}-related events (such as hypermethylation) are reversed after \textit{H pylori} eradication\textsuperscript{34–36} (Figure 3). Any increase after \textit{H pylori} eradication also would reduce overgrowth of non-\textit{H pylori} bacteria and potentially reduce or eliminate their deleterious effects.\textsuperscript{7}

Gastric cancer risk increases with infection with more virulent strains of \textit{H pylori}, such as a CagA-positive strains.\textsuperscript{2} Attempts to associate a specific \textit{H pylori}-related disease with an individual putative virulence factor have produced inconsistent results, possibly because most virulence factors frequently are found together in the more virulent strains.\textsuperscript{2} None of the recognized virulence factors have been associated with a specific disease. However, they typically are associated with an increase in the inflammatory response and possibly can best be considered as markers for the severity of inflammation.\textsuperscript{2} Importantly, all \textit{H pylori} strains cause gastric inflammation and disease; no avirulent strains have been identified. The difference in gastric cancer risk between the most- and the least-virulent strains is probably less than 3-fold, prompting the recommendation that all \textit{H pylori} infections be eradicated, irrespective of virulence factors.\textsuperscript{2,15}

**Clinical Research Findings**

\textit{H pylori} eradication eliminates the noxious stimulus and promotes resolution of inflammation. However, resolution of inflammation is a highly coordinated process regulated by anti-inflammatory molecules, including lipid mediators such as lipoxins and resolvins. This brings up the issue of whether and/or when \textit{H pylori}-induced inflammation has resolved.\textsuperscript{37} Gastric cancer development is associated with inflammation. Increasing our ability to identify whether inflammation has resolved (or not), and why, should provide new insights on factors that determine cancer risk after \textit{H pylori} eradication and help identify strategies to reduce cancer risk further.

People who have undergone removal of an early gastric tumor have a high rate of metachronous cancer, and could provide a high-risk population for clinical studies, which could be performed in a reasonable period of time with a reasonable sample size. For example, this population may be ideal for studies of risk factors for metachronous cancers or for randomized controlled trials of gastric cancer prevention (such as with anti-oxidants, cyclooxygenase II inhibitors, and so forth). These individuals also might be studied to identify biomarkers of disease recurrence and progression.

There is evidence that it might be possible to reverse atrophic gastritis or gastric atrophy. For example, studies performed before \textit{H pylori} was discovered found that corticosteroid therapy for patients with atrophic gastritis or atrophy (autoimmune and \textit{H pylori}-associated diseases) produced a partial recovery of parietal and chief cells.\textsuperscript{38–41} These observations have not been confirmed since patients began receiving \textit{H pylori} eradication therapy. It might be unethical to use high-dose steroid therapy to attempt to reverse atrophic changes, but it might be possible to study patients with atrophic gastritis who receive steroids for other conditions.

Studies in patients and animals receiving tamoxifen showed regression of intestinal metaplasia. Partial reversal of intestinal metaplasia also was observed in animals given adenosine diphosphate ribosylation inhibitors, such as ola-parib, or prostaglandin E\textsubscript{2}.\textsuperscript{42,43} However, prostaglandin E\textsubscript{2} is believed to be involved in the development of colon cancer, therefore it probably should not be given to patients.\textsuperscript{37} Nonetheless, these intriguing findings indicate that it may be possible to at least partially reverse atrophic gastritis.\textsuperscript{42,44} Evidence for a direct role of intestinal

![Figure 3. \textit{H pylori} infection leads to genetic instability of epithelial cells. \textit{H pylori} can induce methylation of multiple CpG islands, and acting through stimulation of nuclear factor-κB (NF-κB) it also stimulates activation-induced cytidine deaminase (AID), which alters nucleotides. Furthermore, the interaction of \textit{H pylori} with the cell can result in double-stranded breaks in DNA, as well as alter the expression of microRNAs (miRNAs) and impair DNA mismatch repair, all of which serve to increase genetic instability. CDS, coding domain sequence; RISC, RNA-induced silencing complex. Adapted with permission from reference Shiotani et al.\textsuperscript{5}](image)
metaplasia or spasmolytic polypeptide-expressing metaplasia in gastric carcinogenesis is circumstantial; it is possible that reversal of atrophy may result in detectable changes (eg, related to transdifferentiation) that do not significantly modify cancer risk.\textsuperscript{45} Studies designed to reverse atrophic changes therefore also must assess changes in cancer risk, such as reduced genetic instability in the involved mucosa.

Finally, whole-genome sequencing analyses of gastric cancers have begun to identify factors that promote gastric carcinogenesis. This information has been used to develop tiered molecular classification systems that relate genetic changes to different etiologies of gastric cancer (eg, \textit{H pylori} or Epstein–Barr virus).\textsuperscript{46,47} These types of studies could lead to better design of cancer treatment and pathogenesis.

**Eradication Therapy**

Reducing gastric cancer from a major clinical problem and cause of cancer death to a rare disease requires that we reliably eradicate or prevent \textit{H pylori} infections. Theoretically, \textit{H pylori} cause a relatively straightforward gastric infection—they are an organism that is susceptible to many antibiotics. Traditionally, studies of antimicrobial therapy for other infections have been performed and interpreted under conditions of well-defined drug susceptibility. In other infectious diseases the development of antimicrobial resistance produced rapid changes in recommendations and practice. \textit{H pylori} has been an exception in that treatment regimens that vary in dose, duration, and composition often are compared, and data have been interpreted without consideration for patterns or effects of drug resistance.

The rapid decrease in efficacy of clarithromycin-containing regimens has produced a clinical dilemma because these are often the only therapies approved by local regulatory authorities. In response to this decrease in efficacy, new combinations of the drugs, such as sequential therapy, were introduced and claimed to be superior. However, in the absence of clarithromycin resistance, the new 4-drug clarithromycin and metronidazole-containing regimens (eg, sequential, concomitant, or hybrid regimens and 14-day clarithromycin triple therapy) all have similar high levels of efficacy. New formulations, such as sequential therapy, contain a third antimicrobial agent (metronidazole or tinidazole), so it can only appear to be superior to triple therapy in populations in which the level of clarithromycin resistance is modest and metronidazole resistance is low. After repeatedly proving that sequential therapy was superior to triple therapy in an Italian population, researchers tested sequential therapy in populations with higher levels of metronidazole resistance and found it to be ineffective (78% eradication in a study in Korea, 85% in a study in France, and 84% in a study in Spain).\textsuperscript{48} A regimen is considered to be effective only if it reproducibly eradicates the infection in 90% or more of the treated patients. Therefore, sequential therapy is not superior to triple therapy in only certain populations.\textsuperscript{48}

The focus on testing for superiority via comparative studies with a regimen known to be ineffective in a specific population (eg, because of clarithromycin resistance), instead of a focus on understanding the mechanisms of efficacy (such as differences in resistance), has delayed our understanding of the factors responsible for the efficacy and failure of the 4-drug combinations by more than a decade. We now recognize that we must collect data on the effects of resistance to each antimicrobial agent, separately and in combination, before we interpret the data on patient outcomes, to determine if the results are generalizable rather than population-specific. During this learning process many thousands of patients were assigned randomly to groups given regimens known to be ineffective in those populations and thereby experienced unnecessary treatment failures and their consequences.

**Lessons Learned**

Study participants are assigned randomly to groups to produce study populations that are equivalent in all respects. In retrospect, in many comparative studies, the outcome was entirely dependent on the pattern of drug resistance in the population studied. In a population with a low prevalence of resistance to 14-day treatment with clarithromycin, 10-day sequential therapy either would be equivalent or triple therapy would be slightly superior. Sequential therapy therefore could be considered effective and superior to other treatments in Italy, yet ineffective in Korea. These results are explained entirely by differences in patterns of drug resistance, which typically were not assessed before studies were initiated. Findings from many, or even most, comparative studies, cannot be applied to other populations unless they are accompanied by resistance data. Meta-analyses have compounded these errors by combining studies from the same geographic location and then making general conclusions about efficacy.

**Potentially Inaccurate Conclusions**

In analyzing the results of any study of antimicrobial agents, it is important to determine the effect of drug resistance on efficacy. Efficacy should be presented in terms of proportions of subjects cured, with 95% confidence intervals. Some comparative trials and meta-analyses provide results in terms of odds ratios and discuss superiority, even though no regimen produced an acceptable cure rate.\textsuperscript{49} To be clinically useful, a reagent must eradicate strains susceptible to the antibiotics tested in at least 90% of subjects. Any claim of superiority from a comparison of 2 otherwise good or excellent treatment regimens must be accompanied by an explanation of an otherwise unexpected result. Differences in effectiveness often appeared because the bacteria were resistant to 1 of the drugs tested.

In the past, claims of superiority often resulted when a new combination was compared with a drug already shown to provide an unacceptably low rate of cure in the study population. The suspicion that investigators may have chosen a known inferior regimen in an attempt to make their study regimen look more effective can be tested by examining the justifications for sample sizes. Randomization reliably would produce study groups that differed in
relation to the effects of resistance on only 1 regimen, therefore there would be no valid hypothesis.

The principles of informed consent also require that potential subjects be informed of all that is known by the investigators and all published information on issues that might influence their willingness to participate (including that they might receive a regimen known to have an unacceptably low cure rate in that population). In 1952, Sir Heneage Ogilvie\(^5\) called the process of disguising (eg, calling an inferior regimen “standard therapy”) or withholding information that might influence participation “medical fraud.” In either instance (ie, no valid hypothesis or lack of truly informed consent) the study would be unethical.\(^5\)

Patient-Specific Therapy

\(H pylori\) eradication therapy is relatively simple; health care workers must consider only drug availability, acceptability (such as whether patients might have allergies or the drugs have side effects), cost, and known or suspected patterns of resistance, based on prior experience with the drug in the same population. Whenever possible, only regimens that reliably yield more than 90%, preferably more than 95%, treatment success should be used. Data on resistance or susceptibility of each patient's infection to the drugs planned to be used should be considered. Pretreatment tests are not widely available, although rapid molecular tests for clarithromycin resistance are practical and commercially available.\(^2\) The best advice for areas where susceptibility tests are not yet available is to use what works reliably locally and then perform a follow up evaluation of patients to ensure eradication of infection and to detect trends of antimicrobial resistance. There are now many regimens available that reliably will provide 95% or greater treatment success per protocol when used to eradicate susceptible strains. These include 14-day therapy with clarithromycin or metronidazole triple therapy, sequential therapy, concomitant therapy, and levofloxacin triple therapy (see Table 1 and Supplementary material).\(^3\)

In most of the United States, resistance to the combination of clarithromycin and metronidazole is rare, making concomitant therapy our first choice. If the patient's infection does not respond to this therapy, bismuth quadruple therapy is given. Infections that are not eradicated by either regimen should be cultured and tested for susceptibility or the patient should be sent to a center with expertise in resistant infections. It is possible to predict the outcome of most therapeutic regimens, provided there is local or regional data available on drug susceptibility (see Supplementary data).

### Table 1. Common Eradication Regimens and Resistance

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Clarithromycin susceptible, %</th>
<th>Clarithromycin resistant, %</th>
<th>Metronidazole resistance, %</th>
<th>Metronidazole–clarithromycin resistant, %</th>
<th>Levofloxacin resistant, %</th>
<th>Population result(&lt;90%) cure(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin triple 7(^c)</td>
<td>93</td>
<td>0–10(^b)</td>
<td>93</td>
<td>0–10(^b)</td>
<td>93</td>
<td>Clarithromycin &gt;4%</td>
</tr>
<tr>
<td>Clarithromycin triple 14</td>
<td>98</td>
<td>0–49(^b)</td>
<td>98</td>
<td>0–49(^b)</td>
<td>98</td>
<td>Clarithromycin &gt;10%</td>
</tr>
<tr>
<td>Sequential 10</td>
<td>94</td>
<td>80</td>
<td>75</td>
<td>0–10(^b)</td>
<td>94</td>
<td>Metronidazole and with dual resistance</td>
</tr>
<tr>
<td>Sequential 14(^c)</td>
<td>98</td>
<td>88</td>
<td>75</td>
<td>0–49(^b)</td>
<td>98</td>
<td>Metronidazole and with dual resistance</td>
</tr>
<tr>
<td>Concomitant 4(^c)</td>
<td>98</td>
<td>97</td>
<td>89</td>
<td>0–49(^b)</td>
<td>98</td>
<td>Only with dual resistance</td>
</tr>
<tr>
<td>Levofloxacin triple 14(^c)</td>
<td>97</td>
<td>97</td>
<td>97</td>
<td>97</td>
<td>0–49(^b)</td>
<td>Levofloxacin &gt;10%</td>
</tr>
<tr>
<td>Bismuth quad 10</td>
<td>93</td>
<td>93</td>
<td>85</td>
<td>85</td>
<td>93</td>
<td>Metronidazole &gt;37%</td>
</tr>
<tr>
<td>Bismuth quad 14</td>
<td>98</td>
<td>98</td>
<td>95</td>
<td>95</td>
<td>98</td>
<td>Adherence issues primarily</td>
</tr>
</tbody>
</table>

NOTE. In the United States, treatment-naïve patients are expected to be resistant to clarithromycin (10%–20%), metronidazole (20%–40%), and levofloxacin (>30%), but not amoxicillin, tetracycline, or rifabutin (<1%). Patients previously treated with a macrolide, metronidazole, or quinolone are expected to have high rates of resistance, therefore susceptibility testing is recommended.

\(^a\)The cure rate for a population will decrease to less than 90% when resistance exceeds the percentage shown using the therapy shown.

\(^b\)Seven-day, 10%; 14-day, 20% success with proton pump inhibitor + amoxicillin was used for calculations when resistance was present because the represent Western populations. Results depend in part on the prevalence of CYP2Y19 polymorphisms because poor proton pump inhibitor metabolism tends to increase treatment success with this dual therapy.

\(^c\)Seven- and 10-day therapies are not recommended because they either are ineffective (levofloxacin) or are less effective (clarithromycin).
that the addition of citric acid, which suppresses the delta over baseline value in uninfected individuals and increases the value in subjects with *H. pylori* infection, should reduce the problem, but this strategy requires direct testing.\textsuperscript{55,56,58} False-positive results lead to the erroneous conclusion that antibiotic treatment failed. This is one cause of what appears to be multiple treatment failures.\textsuperscript{56} As such, in areas where atrophic gastritis is common, patients with results from a $^{13}$C-urea breath test between the cut-off value and a delta over baseline value of approximately 10 should not be considered as treatment failures until the finding is confirmed with a different test, such as a stool antigen assay or histologic analysis. In regions where atrophic gastritis is common and the urea breath test does not contain citric acid, urea breath tests results may be in this gray zone for more than 10% of cases.\textsuperscript{56} Studies are needed to determine whether citric or malic acid adjutant can reduce the frequency of false-positive urea breath test results.

Future studies should provide more data to guide selection of patient-specific therapy. New molecular methods that detect specific resistance using stool or biopsy specimens likely will be developed to allow therapy to be tailored based on susceptibility. We predict a renewal of interest in amoxicillin and high-dose proton pump inhibitor dual therapy. This regimen appears to be highly successful in Asia, but it has fared less well in Western populations. Areas for potential advances include more reliable control of intragastric pH and a better understanding of outcome in relation to amoxicillin pharmacokinetics. Tetracycline continues to be unavailable or difficult to obtain in many countries; studies are needed to learn whether amoxicillin or doxycycline can be substituted reliably. Until such studies are available it is best to still avoid doxycycline. New drugs such as solithromycin eventually could prove useful.

### Is the Only Good *H pylori* a Dead *H pylori*?

Any claim that a major human pathogen also might provide a meaningful health benefit, and that plans to eradicate it should be reconsidered, is guaranteed to elicit interest from the press. *H. pylori* was no exception and the press has continued to carry stories regarding a possible relationship between reductions in *H pylori* infections and the increased prevalence of esophageal adenocarcinoma, childhood asthma, and obesity. *H. pylori* infection has been proposed to protect against these disorders. In this instance, the term *protection* means that there is an inverse correlation in an epidemiologic study. However, because 2 events are associated does not mean that one causes the other. For example, one study\textsuperscript{59} reported a correlation between the number of storks in Brandenburg, Germany, and the birth rate in Berlin.

It could be possible that factors associated with decreases in *H pylori* infection also led to the recognition of unrecognized positive associations. For example, there has long been an interest in a possible role of chronic infection with atherosclerosis.\textsuperscript{60} The journal *Global Heart*\textsuperscript{61,62} devoted a large portion of the June 2014 issue to atherosclerosis in ancient human beings. Computed tomography studies found that ancient human beings had extensive atherosclerosis, even though the people analyzed were from different locations, had a wide range of diets and lifestyles, and died at relatively young ages.\textsuperscript{61,62} The researchers proposed that chronic inflammation induced by microbial and parasitic diseases might have been responsible.\textsuperscript{61,62} The incidence of myocardial infarctions decreased significantly in the second half of the 20th century in the United States, indicating a concomitant change in an important environmental factor(s) involved in atherosclerosis.\textsuperscript{63} Could one of those factors have been *H pylori* infection?

*H pylori* has been with human beings since we traveled out of Africa more than 50,000 years ago.\textsuperscript{5,64} The bacteria have been proposed to cause a variety of extragastric diseases and metabolic derangements, either directly, through molecular mimicry, or indirectly, by producing chronic inflammation.\textsuperscript{55–67} The *H pylori*–related disease peptic ulcer has long been associated with an increased risk for cardiovascular disease.\textsuperscript{68} The decrease in cardiovascular mortality recently was linked with the prevalence of *H pylori* in the United States.\textsuperscript{68} Examination of the hearts of young soldiers who died during the second half of the 20th century (ie, during the Korean, Vietnam, and Gulf wars) showed a progressive decrease in significant coronary atherosclerosis. Over the same time period, there also has been a decrease in the prevalence of *H pylori* infection in the US population (Figure 4).\textsuperscript{70–73} Although these 2 events might be unrelated, *H pylori* infection has been linked with systemic inflammation, atherosclerosis, lipid disorders, heart disease, alterations in vitamin B12 metabolism, and changes in the microbiome. We provide a testable hypothesis that coronary atherosclerosis might be associated with a preventable factor.

### Figure 4. Relationship between coronary artery disease and *H pylori* infection in the United States. Data on coronary artery disease were collected from histologic analyses of autopsies performed on soldiers who died in the Korean, Vietnam, and Middle East wars.\textsuperscript{70–72} They were compared with the prevalence of *H pylori* infection in the US population during the same time periods, based on the premise that infection at age 22 did not change during the lifetimes of this cohort.\textsuperscript{73}
In a review article, Julie Parsonnet\textsuperscript{74} considered the evidence that \textit{H pylori} reduces the risk of immune regulator disorders such as asthma, esophageal cancer, Barrett’s esophagus, gastroesophageal disease, inflammatory bowel disease, infectious diseases such as tuberculosis and gastroenteritis, and obesity. Overall, she was skeptical of the associations and concluded “the mere fact that \textit{H pylori} is disappearing from the human host without substantive intervention might indicate that, in many countries, it is providing little benefit.”\textsuperscript{74}

\textbf{Esophageal Disease}

The role of \textit{H pylori} in the development of esophageal adenocarcinoma, Barrett’s esophagus, and gastroesophageal reflux disease was discussed in the most recent Maastricht consensus report (see Malfertheiner et al\textsuperscript{75}). These esophageal problems are all acid reflux–related diseases. \textit{H pylori} infection can promote and inhibit acid reflux; antral predominant gastritis is associated with increased acid secretion and an increased risk for reflux esophagitis, whereas \textit{H pylori}–induced corpus gastritis reduces acid secretion and thereby prevents or reduces the severity of reflux. According to the model, the bacterium behaves as a biologic secretory or antisecretory agent\textsuperscript{76,77} that promotes, prevents, or has no effect on gastroesophageal reflux, depending on the pattern and extent of gastritis. Importantly, the more \textit{H pylori} reduces acid secretion, the more protection it provides against acid reflux and the greater the risk of gastric cancer. Gastric cancer is a common disease that affects all races and both sexes and, until the mid-20th century was the leading cause of cancer deaths worldwide. Esophageal adenocarcinoma is primarily a rare disease of white men (ie, the incidence of esophageal adenocarcinoma is more similar to that of small-bowel adenocarcinoma) (Figure 5).\textsuperscript{78} Despite the continuing decrease in the incidence of gastric carcinoma in the United States, the risk of developing adenocarcinoma of the stomach remains higher than the risk of adenocarcinoma of the esophagus in the highest-risk group (ie, men in the United States) (Figure 6).\textsuperscript{79}

\textbf{Nonesophageal Diseases}

Ptolemy proposed that the earth was the center of the universe. He had observed that when he looked at the northern sky he (and everyone after him) saw that the stars circled around the earth. Thomas Henry Huxley said in 1870 “The great tragedy of science is the slaying of a beautiful hypothesis by an ugly fact.” Although thousands of experiments can support a hypothesis, it only takes 1 finding to disprove it. For example, despite countless observations over more than a thousand years that supported Ptolemy’s model, experiments performed with the first telescopes rapidly disproved it. We therefore will not review each association for validity but provide evidence that \textit{H pylori} infection does not cause nonesophageal diseases such as asthma or obesity.

\textbf{Asthma}

The initial studies relating \textit{H pylori} prevalence with asthma were based on the concept that the incidence of asthma was increasing and it would be useful to search for the cause.\textsuperscript{80} The most recent studies found that asthma incidence has peaked or is decreasing.\textsuperscript{81,82} A study of asthma trends in England from 2001 to 2005 involved 333,294 individuals from all socioeconomic groups and all ages. Their results can be used to test whether there was a link between \textit{H pylori} infection and changes in asthma incidence.\textsuperscript{82} The United Kingdom, as a developed country, has experienced a steady reduction in the prevalence of \textit{H pylori} infection, which currently likely is concentrated in immigrants and the lower socioeconomic strata. We therefore predict that any changes related to the decrease in

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Incidence of cancers in the United States. Incidence values are based on data collected in 2011 by the Surveillance, Epidemiology, and End Results Program.}
\end{figure}
H pylori infection would tend to be concentrated in the higher socioeconomic strata. In that study, the incidence rate of asthma decreased significantly in all groups over the interval studied (from 6.9 per 1000 patient-years; 95% confidence interval [CI], 6.8–7.0 to 5.2 per 1000 patient-years; 95% CI, 5.1–5.3) (P < .001).

The decrease occurred in all socioeconomic groups, as assessed by deprivation quintiles. For example, the incidence in quintile 5 (the least affluent and most likely to have H pylori infection) decreased 24.2%, from an age-standardized rate per 1000 patient-years in 2001 of 8 (95% CI, 7.7–8.2) to 6.0 in 2005 (95% CI, 5.8–6.2); whereas in quintile 1 (the most affluent), the incidence rate decreased 26.5%, from 6.3 (95% CI, 6.1–6.5) to 4.6 (95% CI, 4.4–4.8). The greatest effect was in children younger than 5 years of age (a decrease of 38.4%). A decrease in childhood asthma, compared with other developed countries, also has been observed. Overall, these data are not consistent with the hypothesis that H pylori infection protects against childhood asthma.

The asthma association studies led to studies in mice showing that H pylori infection protected against asthma, possibly by promoting immune tolerance. Further studies showed that 2 H pylori antigens (γ-glutamyl transpeptidase and VacA) induced T-regulatory cells in the gastric mucosa of mice, resulting in the development of tolerance and reduced allergic responses. Of interest, induction of T-regulatory cells in the gastric mucosa is also an important step in the establishment and maintenance of H pylori–induced gastric adenocarcinoma.

Overall, animal studies showed that H pylori possess specific antigens that might mediate alterations in the immune system to promote tolerance and reduce asthma. An alternate possibility is that because H pylori infection correlates with poor household hygiene, any protection observed likely was related to differences in household hygiene (the hygiene hypothesis), with the presence of H pylori serving as a marker for poor household hygiene. This hypothesis has been tested in vivo and in vitro. The first test was designed to separate H pylori from other elements in the hygiene hypothesis. In Malaysia, very few Malay people have H pylori infections, however, in many areas, hygiene is substandard. According to the H pylori hypothesis, childhood asthma should be a common problem among the Malay because of the absence of H pylori, however, it is not.

A second test included mouse models and was designed to examine the observation that the presence of dogs in a home was associated with a reduced risk of asthma. Investigators collected house dust from a residence with a pet dog and from a residence with no pets and used the 2 house dust samples to try to protect mice from asthma. The dust from the family with the pet dog protected mice from asthma, and was associated with remodeling of the gut microbiome related, at least in part, to the presence of Lactobacillus johnsonii. The investigators concluded that protection against asthma is likely a combinatorial effect based on multiple pathways and resulting microbial products encoded by co-colonizers resulting in presentation of a specific suite of microbial ligands and a distinct profile of microbial metabolites to the innate and acquired components of the host immune system.

For a more detailed discussion of models of asthma, differences in the immune responses of mice vs human beings, and roles of environmental factors (diet and commensals) in allergy and asthma development, see the article by Renz et al. Overall, the studies do not support the hypotheses that increases in childhood asthma were related to the absence of H pylori or reduced immune system stimulation by specific H pylori antigens. One therefore must conclude that the hypothesis is wrong.

**Obesity**

Obesity is an extremely complicated problem. Fundamentally, obesity develops via an imbalance between energy intake and expenditure. In the 20th century, there were enormous changes in the production and availability of food, related to the green revolution, to increases in standards of living, and to improvements to the transportation infrastructure. Giant companies began producing calorie-dense processed foods, sugary soft drinks, and fast foods, while the proportion of the population that performed intensive physical work decreased. In 1939, Prentice wrote “Hunger and History,” in which he reviewed the world’s literature on hunger from antiquity to the 1930s, discussing famines, hunger, and food production. He stated that a history of hunger had become possible because for the first time the world had entered a phase in which there were large regions without risk of famine.

This book was followed in 1952 by “The Geography of Hunger,” in which Josue de Castro examined the problem of world hunger (two thirds of the world’s population was thought to suffer from hunger at that time). He related a study by Rigoberto Aguillar, who in 1944 examined 10,000 poor children in Mexico City. Aguillar found 5000 children to have clear signs of dietary deficiency; children age 10 to 12 years appeared to be no older than age 4 or 5. In 1945, de Castro visited Mexico City where he found “innumerable cases of vitamin deficiency in children.” A half century later the problem had changed to an increasing concern about obesity among Mexican children.

It has been proposed that increasing widespread obesity might be related to alterations in gastric physiology, caused by the absence of H pylori. However, there are little data to support that hypothesis other than conflicting data from comparisons of obesity rates among those with and without H pylori infection. Obesity is a manifestation of an imbalance between energy intake and expenditure, so the absence of H pylori might increase appetite and intake. However, it not clear whether the absence of H pylori also might encourage behaviors that reduce energy consumption.

The natural decrease in the prevalence of H pylori occurred first in the proportion of the population with high socioeconomic status, and that decrease continues among people of low socioeconomic status, especially during childhood. The infected and uninfected populations differ in
many ways, some of which might affect obesity. These differences include the consumption of processed foods and high-calorie fast foods, as well as in the amount of physical activity. Available studies rarely have considered variables other than \textit{H pylori} prevalence and body mass index, and none have taken into account the marked changes in the food industry and its effects on eating habits.

The food industry has had remarkable effects on human behavior (eg, on a mother’s choice of breakfast food for her school-aged children). The industry steadily has improved its ability to produce delicious high-calorie foods. Innovations that encourage consumption include the discovery of bliss points, and how to combine ingredients to largely negate satiety signals, which normally limit consumption. These innovations by the food industry have resulted in increased consumption of processed foods that are dense in sugar and fat, and of extra calories contained in soft drinks and fast foods. The modern lifestyle also encourages sedentary activities as a result of television, computers, video games, and smart phones, all of which also increase opportunities to snack. In addition, overall physical activity has decreased (ie, most ride rather than walk).

\textit{H pylori} infection has long been rare among Malays (\sim 60\% of the population of Malaysia), but was common and now is decreasing among Chinese (\sim 30\% of the population) and Indian (\sim 10\%) subpopulations. Malaysia might be considered a poster child of a developing country because it has undergone rapid industrialization and urbanization with rapid increases in standards of living. However, these changes have been associated with Westernization of their diet, increased caloric intake, and reduced energy expenditure. The change to a sedentary lifestyle with increased intake of calorie-dense foods (eg, McDonald’s [McDonald’s Corporation, Oak Brook, IL] entered in 1982, Pizza Hut [Pizza Hut, Inc, Plano, TX] in 1984, and Domino’s Pizza [Domino’s, Ann Arbor, MI] in 1997) has resulted in an increasing prevalence of obesity (eg, 0.7\% in 1990 to \textgreater 10\% in 2004), and this has occurred among the Malays, Chinese, and Indians, irrespective of differences in \textit{H pylori} prevalence. The recent increase in obesity is a complex issue and there is only weak circumstantial evidence for a significant role of decreasing \textit{H pylori} infection in the obesity epidemic. A meaningful causative association between \textit{H pylori} and obesity is unlikely.

**Supplementary Material**
Note: To access the supplementary material accompanying this article, visit the online version of \textit{Gastroenterology} at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.01.040.

**References**


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Conflicts of interest
The author discloses the following: The author is an unpaid consultant for Novartis in relation to vaccine development for the treatment or prevention of H pylori infection, is a paid consultant for RedHill Biopharma regarding novel H pylori therapies and for Otsuka Pharmaceuticals regarding diagnostic testing, and has received royalties from Baylor College of Medicine patents covering materials related to the 13C-urea breath test.

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Supplementary Materials

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 gastroduodenal structure and function. In addition, the outcome for an individual patient is unpredictable and at least 20% of patients 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 in regions of China.1 In the United States in the 1970s, when H pylori still was 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 and more than 4,000,000 hospital days devoted to the treatment of peptic ulcer. In addition, there were 140,000 surgeries per year, and 9,000 hospital deaths per year.2 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 likely has been responsible for the inability of a recent epidemiologic study using NHANES III data to show an increase in all-cause mortality among those with presumably asymptomatic H pylori infections.3 The most recent focus has been on H pylori eradication as a means of eradication of gastric cancer, which is a major cause of cancer deaths. As noted previously, the strategy to accomplish this goal will differ regionally depending on the prevalence and risks in different populations. The United States has been experiencing a 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 likely is manifest as the increase in the rate of distal gastric cancer in Caucasians of both sexes in the 25- to 39-year-old age group reported during the past 3 decades.4 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. We discuss how reliable treatment success can be achieved.

Approach to Treatment Outcome Estimation

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 a population if the pattern of resistance is known. This currently is true for triple therapies and clarithromycin-containing 3- and 4-drug non–bismuth-containing regimens. Data remain insufficient for bismuth quadruple therapy. The basic formula is as follows: the proportion of patients with susceptible strains times the success rate (eg, 98%), plus the proportion of patients with resistant strains times the success rate with resistance (eg, 10%).5,6 One only needs a table (such as Table 1) showing the cure rates in relation to antimicrobial susceptibility (ie, all susceptible, resistant to each single antimicrobial, and resistant to combinations of antimicrobials) (Table 1).

Examples

Seven-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 patients with clarithromycin resistance. In a comparative trial of 200 patients (ie, 100 patients with no resistance and 100 patients from the population), we could have 100 susceptible vs a population with 87 with susceptible strains and 13 with resistant strains. The simple calculation would be as follows: 100 × 94% (considering a 94% success rate for susceptible) vs (94% of 87) plus (10% of 13) = 98.712 + 1.3 = 83.6. Thus, the authors would report superiority with 94% vs 83% (P < .001). However, because the outcome was assured before starting the study there could be no valid hypothesis (no clinical equipoise). Such studies continue to be published (eg, Park et al).

Ten-day sequential therapy. This 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) as follows: (number of none resistant) (95%) + (number of clarithromycin resistant) (80%) + (number of metronidazole resistant) (75%) + (number of dual resistant) (10%) or (57 × 0.95) + (10 × 0.80) + (30 × 0.75) + (3 × 0.1) = 54.1 + 8 + 22.5 + 0.3, resulting in 84.9% success pre-protocol. The actual result in a clinical trial likely would be somewhat lower because of issues with adherence (ie, intention-to-treat result). Fourteen-day sequential therapy would provide an improved result. However, 14-day concomitant therapy would provide a much better outcome (ie, at least 94% per protocol), which is why sequential therapy now is considered obsolete.

Other Drug Combinations

This type of calculation is effective for regimens in which the success is known specifically in relation to the presence of resistance. Antimicrobials used in triple therapies that become ineffective in the presence of resistance such as fluoroquinolones (eg, levofloxacin), clarithromycin will provide reliable results and one can use the table in references for individual data. There still are 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. In the few countries where tetracycline resistance or amoxicillin resistance are problems, these calculations should be used with caution and data on the effect of this resistance should be collected. Because countries where a significant proportion of the population are slower proton pump inhibitor–metabolizers, related to CYP2C19 genotypes, the results with the dual amoxicillin and proton pump inhibitor 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 reported earlier showed a per-protocol result of approximately 83%. This was the result with that specific population. None of their or your patients will achieve 83% because the cure rates were 94% for susceptible patients and 10% (actually probably closer to 0%) for patients with resistant strains. If your patient has received macrolides previously, the odds are they will be in the 0%-10% rate of success group. **Supplementary Table 1** shows the effect of resistance on the outcome of 7- and 14-day clarithromycin triple therapy. The proportion of patients who fail and require re-treatment can be estimated as approximately 100 minus the intention-to-treat success rate and thus the results in **Table 1** are optimistic. In the best scenario, treatment success with 7-day triple therapy would decrease to less than 90% (the cut-off value for an acceptable therapy) with 5% clarithromycin resistance; 14-day therapy would become unacceptable at 10% resistance. If one knows the resistant pattern in their patient 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 probably is 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.

**References**

Supplementary Table 1. Effect of Clarithromycin Resistance on Outcomes (Per Protocol) of Clarithromycin-Containing Triple Therapies

<table>
<thead>
<tr>
<th>Resistance (%)</th>
<th>7-day result (%)</th>
<th>14-day result (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>89.8</td>
<td>93.1</td>
</tr>
<tr>
<td>10</td>
<td>85.6</td>
<td>89.3</td>
</tr>
<tr>
<td>20</td>
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<td>79.6</td>
</tr>
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<td>40</td>
<td>60.4</td>
<td>62.2</td>
</tr>
<tr>
<td>80</td>
<td>26.8</td>
<td>27.4</td>
</tr>
</tbody>
</table>

NOTE. Assumes a 10% success rate with the dual amoxicillin per-protocol component alone.