**Helicobacter pylori** Diagnostics and Treatment: Could a Lack of Universal Consensus Be the Best Consensus?

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*Helicobacter pylori* testing and treatment has become a subject of intense debate and confusion worldwide in recent years, for both laboratory scientists and clinicians. The gastric pathogen *H. pylori* is believed to infect up to half of the world’s population disproportionately, yet it remains a challenging diagnosis for many physicians worldwide. New testing mechanisms have been introduced, but no single universal approach for testing and treating *H. pylori* has been established to date. In effect, no population on earth has been spared from these chronic infections, but regional differences in prevalence and associated disease severity do exist. Not unexpectedly, there also exist regional approaches in the diagnosis, treatment, and management of these patients. This Q&A article borrows the experience of 3 international experts in the field of *H. pylori* to reflect on the current status of *H. pylori* management and challenges on 3 separate continents, specifically Australia, Europe, and North America.

Several different guidelines exist for the diagnosis/treatment of *H. pylori* infections. What controversy or challenges do you perceive with current guidelines?

**Barry Marshall:** Guidelines for the treatment of *H. pylori* infections are aimed toward achieving a cure rate of at least 85%. In the last 10 years, because of gradually increasing resistance to macrolides, the very successful and popular combination treatment using a proton pump inhibitor (PPI), clarithromycin, and amoxicillin has declined in effectiveness from greater than an 85% cure rate originally, to the region of 70%–80% in some areas where long-acting macrolides have been used for 10 or more years. This has created research interest in the evaluation of newer and more intensive therapies, often with extra antibiotics added to hopefully eradicate the *H. pylori* without the emergence of resistant isolates. Over the years, shorter and more-intensive treatments for *H. pylori* infection have been tried, and these are probably worthy of further investigation. Some of these treatments have high cure rates of *H. pylori* within 5 days. In most cases, at least 7 days of treatment were required, and the original triple therapy mentioned above was found to be quite successful in the UK and Australia in a 7-day course, with no difference between 10 and 14 days in prospective studies. Therefore, in Australia a 7-day treatment was advocated. In the US, however, there was a difference between 7 and 10 days but no significant difference between 10 and 14 days of therapy. Therefore, in my opinion one would try to achieve the highest cure rate in the greatest number of patients with a duration of treatment that was not excessive but certainly not too short. Ultimately, my choice is to use a 10-day therapy. To avoid the high doses of concurrent antibiotics for long periods of time, clinicians have devised sequential therapies. Two strategies exist here. Strategy 1 is to give some antibacterials for the first half of the treatment and switch to completely different ones in the second half. Sequential therapy consists of a PPI with amoxicillin for the first 5 days and then clarithromycin with metronidazole and a PPI for the next 5 days. This approach has a high cure rate and is relatively cost-effective. Many variations on this plan have evolved, and in my clinic we decided that since amoxicillin...
Sequential and complicated therapies in patients for whom recent treatment failed are problematic for physicians, general practitioners, and government health authorities, because they often need to be customized, depending on the previous treatment of the patient, and clearly require careful motivation and compliance by the patient. Therefore, they may best be saved for specialty clinics with experience in treating \textit{H. pylori} infections. In Australia, this situation is partially resolved by making these “exotic” combinations of antibiotic treatments available from the government health authorities. Nevertheless, the exotic therapies can be used with considerable success, and nearly all \textit{H. pylori} patients can be successfully cured without too much inconvenience. The controversy with the current guidelines may be related to the pros and cons of different antibiotic combinations in different countries and perhaps to the decision by the managing doctor whether antibiotic sensitivity testing (i.e., endoscopy and biopsy) is required to collect further detailed information on the patient’s infection before customized therapy can be initiated. In my opinion, this final issue is probably best left up to the managing physician, depending on the resources available in that clinic.

Karen Goodman: The guidelines are based on summaries of published results of clinical trials and other relevant clinical studies and do not adequately account for the substantial variation known to occur across populations with respect to geography and/or socioeconomic status. The guidelines may be relevant more or less to the locations represented by the experts who developed them, but they are often adhered to by policy makers elsewhere when local guidelines are lacking. This is a problem because the variations across populations are more complex than just dividing the world into developed and developing countries, or East and West. A better, though not perfect, way to divide the world with respect to this variation is to separate populations with high and low \textit{H. pylori} prevalence. For example, my work in the Canadian Arctic and that of colleagues in Alaska show that high-prevalence populations located within developed countries have \textit{H. pylori} infection management and control issues similar to those encountered in the developing world. However, there will remain differences in the cost-effectiveness of specific clinical approaches owing to other differences, including bacterial strain susceptibility to therapy, the ability of individuals to adhere to complex therapies, other host factors that influence treatment effectiveness, rates of peptic ulcer disease and gastric cancer in the absence of treatment, costs of preventive measures, and costs of treating disease in the absence of preventive measures. A systematic review of clinical trials showed inadequate performance of therapies recommended in many authoritative guidelines (triple therapies that include clarithromycin), even in the locations targeted by the recommendations. As a result, the review authors encouraged clinicians to ignore irrelevant guidelines and use what works locally, which highlights a gap in the evidence given that trial-based evidence to identify what works locally is not available for most locations.

In Canada, guidelines generated by the Canadian \textit{Helicobacter} Study Group in the past decade have influenced practice across the country. New physicians have been educated according to these guidelines, and provincial and territorial healthcare systems have based \textit{H. pylori} management policies on them. The motivation for the Canadian North \textit{H. pylori} (CANHelp) Working Group, which I formed with colleagues to begin community-based \textit{H. pylori} research projects in the Northwest Territories in 2007, was the widespread perception among healthcare providers and affected community members that the current \textit{H. pylori} management practices based on Canadian guidelines were not effective at managing an infection that increases the risk of gastric cancer (which is known to occur at higher rates in indigenous Arctic communities). Our current research, now taking place in communities in the Yukon and Northwest Territories, aims to generate local evidence that healthcare policy makers can use for more effective management of \textit{H. pylori} infection and associated disease.

The initial identification of the high prevalence of \textit{H. pylori} infection in an indigenous Arctic population came from researchers with the CDC Arctic Investigations Program in Alaska. Since then, similar findings have been reported for Greenland, Canada, and Siberia. Investigators working in these areas are currently linked through the Circumpolar \textit{H. pylori} Working Group, in which I represent Canada. Motivated by Brian MacMahon of the Alaska Health Department, this group has drafted recommendations for \textit{H. pylori} management in high-prevalence populations, which we hope to publish. Guidelines issued by the CDC unit...
in Alaska to educate physicians trained in the mainland US and practicing medicine in Alaska native communities differ from Canadian and other Western guidelines, in that a test-and-treat approach is not recommended for patients presenting with dyspepsia. This is due to the high prevalence of *H. pylori* among Alaska natives (around 80%), the poor effectiveness of treatment, and relatively high reinfection rates. Even within this circumpolar group, we have noted some internal regional variation in the prevalence of *H. pylori*, antibiotic susceptibility, and reinfection rates. For this reason, we have attempted to make the recommendations robust to variation from place to place and to the availability of local information.

Serology is widely used in the US to diagnose *H. pylori* despite practice guidelines and many medical insurance companies discouraging its use. Why has serological testing remained a standard testing method, and what role does it play in the diagnosis of *H. pylori* infections?

**Barry Marshall:** Serologic testing for *H. pylori* is sensitive but not as specific as other “direct” diagnostic tests, such as breath tests and biopsy tests. Serology measures IgG antibody in the blood, so it detects the presence or a history of *H. pylori* infection. Often, low concentrations of IgG remain for many years after the eradication of *H. pylori*, and when *H. pylori* has been treated in the past year or two, moderate concentrations of IgG may persist for many months. This is useful information, because in the patient being investigated for the first time for *H. pylori* and who has not had recent antibiotic treatments specifically for *H. pylori*, a positive serologic test indicates a probable *H. pylori* infection, and the physician may choose to proceed with treatment on the basis of that test alone. Once the patient has been treated on one occasion for *H. pylori*, a positive serologic test is of very little use, since it is likely a false positive. Because of the popularity of treating *H. pylori* and because of the many strong antibiotics in common use, in Western countries there are many patients who still have the antibody but in whom *H. pylori* has been eradicated either accidentally or deliberately. These patients make up about 15% of those with positive serology. Therefore, at the very least in serologically positive patients, a confirmatory noninvasive test such as the breath test or even a stool test may be performed in patients before the treatment is commenced. Recognize that about 15% of serologic test results are false positives, and in countries where *H. pylori* prevalence is rather low (such as Australia, where it is 20%), at least one-third of treated patients will not actually have *H. pylori*, if serology alone is used for diagnosis. Follow-up tests should always include a test for actual *H. pylori* infection, such as the urea breath test (UBT) or the stool antigen test (SAT) or, if endoscopy is being contemplated, biopsy tests of the gastric mucosa.

**Francis Mégraud:** *H. pylori* serology is an indirect method of detection and, as any serology, can lead to a false negative in cases of weak immunological response at the extreme ages of life or in cases of immunodeficiency. Furthermore, false-positive results can be seen if cross-reacting antigens are present or, taking into account the half-life of immunoglobulins, if a recent eradication occurred. A large number of kits with various accuracies are on the market. It may also be that antigenicity varies among strains from different ethnic groups. Furthermore, studies testing the accuracy of serological tests were performed in comparison to reference tests, sometimes with suboptimal performances (e.g., the lack of specificity of serology observed was, in fact, due to the lack of sensitivity of the reference method). And, when systematic reviews were performed, all of the studies were mixed without taking into account the type of kit and the reference used, leading to a poor outcome.

Serology has the important advantage of being a noninvasive method that is easy to perform. In recent years, more and more patients are taking over-the-counter PPIs when they suffer from dyspepsia and seek medical attention only if the symptoms persist. PPIs do not eradicate *H. pylori* but lead to an important decrease in the bacterial load, which greatly decreases the sensitivity of the direct methods of *H. pylori* detection, leaving serology as the only valid method. As highlighted in recent guidelines, serology still plays an important role for the pretreatment diagnosis of *H. pylori* infection and not for follow-up after treatment, because the antibodies persist for months or even years after eradicating the bacteria. There are also other specific situations where serology is of interest, e.g., in the case of atrophy, mucosa-associated lymphoid tissue lymphoma, or gastric carcinoma, when the bacteria are reduced to below the threshold of detection by the other methods. However, given the variability in serological kits as recently published, it is imperative to use those with the best accuracy.

**Karen Goodman:** Not all medical insurance companies discourage the use of serology. For example, in the Yukon Territory serology is the only covered *H. pylori*–testing method, and I believe this to be true in some
Canadian provinces. Until recently, other methods were not widely available. In many areas, the SAT is not generally available to healthcare practitioners. In Alberta and the Northwest Territories, all healthcare providers must use the same laboratory to process the UBT, and they do not consider the test valid for children 5 years of age and under, although there is no doubt that it is more valid than serology for diagnosing H. pylori in this age group.

I would consider the lack of availability of other methods to be a major driver for the continued use of serology, as well as the much lower cost of serology relative to other methods. There is also greater infrastructure in typical clinical care settings (and research settings) for collection of blood samples and use of serological assays relative to the infrastructure required for collection of stool samples for the infrastructure required for the collection and, especially, the analysis of breath samples. All of this combined makes serology more convenient than other methods for most clinical care settings.

In addition, many H. pylori experts believe that serology is an adequate testing method for older children and adults who have not been treated recently to eliminate H. pylori infection. This belief likely stems from early H. pylori studies, many of which showed a high correlation between seropositivity and indicators of active infection. These were generally studies of adults, most of whom would have been infected for decades, in an era when H. pylori infection had not been widely targeted for treatment. It is my impression that recent studies show more evidence of substantial proportions of people who are seropositive for H. pylori but negative on indicators of active infection, but I am not aware that this has been demonstrated in published systematic reviews.

Studies have shown similar performance characteristics for the UBT and fecal-antigen ELISA, while others have described specific populations in which one method outperforms the other. Should these tests be used interchangeably?

Francis Mégraud: UBT has become almost a reference method for H. pylori detection. It has the advantage of not being dependent on the transport conditions of the breath sample (in contrast to culture) or on human interpretation (in contrast to histology or the rapid urease test). A SAT using a monoclonal antibody and an ELISA format, in contrast to an immunochromatographic method, has an accuracy close to the UBT. The use of one or the other of these tests is, in fact, more linked to convenience, availability, and cost. In many settings, adult patients are reluctant to give stools and prefer a breath test. The situation may be different for children, who may have difficulty blowing into a tube, while it is easy for the parents to get a stool sample for analysis. In elderly patients, the situation is totally different because, due to frequent constipation, the sensitivity of SAT may be altered. In conclusion, the tests may be used interchangeably except at the extreme ages of life.

Karen Goodman: The variation in agreement of these tests across populations suggests that we should not assume they are equivalent measures of H. pylori infection in the stomach. It is likely that there are instances when H. pylori organisms pass through the digestive tract without colonizing the stomach, a situation that could explain a person having a positive SAT and a negative UBT. Additionally, there is evidence suggesting that H. pylori organisms colonizing the stomach may not shed continually, a situation that could explain a person having a positive UBT with a negative SAT. It is not surprising that there is some disagreement between these tests, because one (UBT) detects the organism in its typical niche and the other (SAT) detects the organism when it is leaving the host. Also, the organism must be alive for the UBT to be positive, but this is not required for the SAT to be positive. Logistic factors must be considered when determining which of these tests to use. Some experts believe the SAT is more accurate for infants and preschool children and prefer it for this age group. In my own research, I have found that stool samples are much harder to collect in the field than breath samples, and so I have always preferred the UBT in community settings. Given that each method has its strengths and weaknesses, some experts recommend using more than one or repeating the same one multiple times. Whether test or combination of tests is adopted, it is best to interpret results according to what the test actually measures (e.g., urease secretion by live bacteria—which may or may not be H. pylori in the stomach; H. pylori antigens in stool—which may or may not be from live bacteria and may or may not have colonized the stomach).

Barry Marshall: The UBT is highly specific, because it measures the enzyme urease in the gastric mucosa, and the difference between a negative test (results approaching close to 0) and positive tests (quite high for labeled CO₂ excretion) is so marked that usually a crystal-clear differentiation is found between negative and positive patients. The SAT should also give a negative or positive result, but the feces-based test measures the output several meters downstream from the stomach. Therefore, there is a less clear breakdown between the antigen signal in a negative patient vs. a positive patient. Therefore, the SAT relies on a cutoff that
There is growing concern about drug-resistant H. pylori, particularly against antibiotics included in standardized triple/quadruple therapies (e.g., macrolides, metronidazole). What is driving this resistance? Are there any viable therapeutic alternatives?

Francis Mégraud: The growing concern about resistance of H. pylori to some antibiotics is justified, especially for macrolides and fluoroquinolones, but not for metronidazole. H. pylori is acquiring resistance essentially by point mutation and not by acquisition of mobile elements. These point mutations are supposed to occur spontaneously and then be selected for when the bacteria are exposed to the corresponding antibiotic. The global population of H. pylori in a stomach may have some macrolide-resistant bacteria. If this population is exposed to a macrolide, the susceptible organisms will be destroyed and the resistant ones will be selected for and emerge as a full population of resistant organisms. The same is true for fluoroquinolones, levofloxacin being the antibiotic of choice against H. pylori in this group, but the gene concerned is different. The selection of resistant mutants is even easier with quinolones than with macrolides, because the mutation frequency is higher.

In both cases, it is possible that the resistant mutant has a different fitness compared to the so-called wild type. In other words, if it is costly to the organism to maintain this resistance, resistant mutants can disappear when the selective agent is not there anymore. But it is also possible that the bacterium gets compensatory mutations in other places on the genome, which will allow the conservation of the mutation, as happens for macrolides.

In reality, the selection of resistant mutants occurs essentially because macrolides or fluoroquinolones are prescribed as the only antibiotic for respiratory tract or urinary infections, and the subinhibitory concentration obtained in the gastric mucosa is the best condition to select for resistant mutants.

The situation with regard to metronidazole is different. First, there is a lack of reproducibility in testing this drug in vitro, even in the same laboratory. This may be due to the importance of the redox potential (critical to reduce the prodrug metronidazole in hydroxylamine), a parameter that is not controlled. Second, there is a lack of clinical correlation between the minimum inhibitory concentration observed and the clinical outcome. Quite often and despite the high minimum inhibitory concentration, H. pylori eradication occurs. This can be explained by the synergy with the other antibiotic and by the high concentration obtained in the mucus when the treatment is prolonged. For these reasons, testing for metronidazole resistance is not recommended anymore.

Two main alternatives have been proposed. The first is to use the antibiotics sequentially. It has been shown that giving the triple therapy (PPI–clarithromycin–metronidazole) after 5 days of PPI–amoxicillin eradicates many clarithromycin-resistant strains. Indeed, the first treatment greatly decreases the bacterial load, including resistant bacteria, allowing the second treatment to be effective. The second is to use a combination of antimicrobials not affected by the resistance problem, i.e., the bismuth-based quadruple therapy. Studies have shown that a special drug, Pylera, containing bismuth salts, tetracycline, and metronidazole given for 10 days with a PPI leads to a high eradication rate, even if the strain appears to be metronidazole resistant in vitro.

Barry Marshall: Because of the widespread use of antibiotics such as metronidazole, macrolides, and quinolones for the eradication of H. pylori, we do see a gradual increase in resistance of H. pylori to these antibiotics. Luckily, however, H. pylori always remains susceptible to amoxicillin, bismuth, furazolidone, and (almost always) tetracycline. Once these rules are understood, there are several alternative treatments that can be used to eradicate H. pylori infections that have failed previous therapies. The rule of thumb is that the 4 antibacterials mentioned immediately above can be reused in different combinations, often with a PPI, to broadly suppress H. pylori. Therefore, one or more of the antibiotics that induce resistance due to mutations can be used in addition to the suppressive therapy to mop up the remaining H. pylori. Thus, treatments such as PPI, bismuth, tetracycline, and metronidazole are particularly effective and useful for persons who are allergic to penicillin. Conversely, the addition of 2 extra drugs, such as ciprofloxacin and rifabutin, to a suppressive therapy of PPI and amoxicillin results in very high cure rates with reasonably cost-effective therapies.

Resistance is probably driven by widespread use of powerful antibiotics in the community, in doses that are not H. pylori–idal but that expose the large popu-
lation of gastric *H. pylori* organisms to a noneradicative antibiotic. There are viable therapeutic alternatives, so that most patients (even those allergic to penicillin) still have the possibility of 3 or 4 different treatments with cure rates of 80%. Thus, there is reason for optimism, although this should be tempered with concern and careful conformity with the recommended and proven guidelines of therapy.

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