REVIEW

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Helicobacter pylori Infection: An Update for the Internist in the Age of Increasing Global Antibiotic Resistance

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ABSTRACT

Helicobacter pylori infects approximately half the world's population and is especially prevalent in the developing world. *H. pylori* is an important cause of global ill health due to its known etiological role in peptic ulcer disease, dyspepsia, gastric cancer, lymphoma, and more recently, recognized in iron deficiency anemia and idiopathic thrombocytopenic purpura. Increased antibiotic usage worldwide has led to antibiotic resistance among many bacteria, including *H. pylori*, resulting in falling success rates of first-line anti-*H. pylori* therapies. Eradication failures are principally due to resistance to clarithromycin, levofloxacin, and metronidazole. Several new treatment options or modifications of established regimens are now recommended by updated practice guidelines for primary or secondary therapy. Because these updated recommendations were published in the gastroenterological literature, internists and primary care physicians, who commonly manage *H. pylori,* may be unaware of these advances. In this review, we outline the changing epidemiology of *H. pylori*, advise on diagnostic test selection for patients not undergoing endoscopy, and highlight current management options in this era of growing antibacterial resistance.

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INTRODUCTION

Helicobacter pylori remains one of the most common causes of peptic ulcer disease, as well as causing dyspeptic symptoms in patients who are not found to have ulcers at endoscopy (nonulcer or "functional" dyspepsia).[1] While gastroenterologists may be most familiar with *H. pylori* and may be consulted for optimal management, the diagnosis of *H. pylori* infection is often made by primary care or internal medicine physicians, who may not be aware of the variety of diagnostic tests available, and that the treatment for *H. pylori* is becoming more challenging due to increasing antibiotic resistance. Falling eradication rates have prompted several authorities to recently update their treatment guidelines for empiric first-line and subsequent therapies.[2-4]

A translation gap exists for the application of knowledge about *H. pylori* to patient care, especially outside specialist practice. For example, while it is well appreciated that *H. pylori* testing is indicated in patients on chronic nonsteroidal anti-inflammatory drug therapy or with a diagnosis of a gastric mucosa-associated lymphoid tissue lymphoma, <20% of such patients with these conditions were investigated for *H. pylori* by their physicians, according to some recent reports.[5,6] In another study, only 54% of US primary care physicians used a "test and treat" strategy seeking *H. pylori* as a cause for dyspepsia, and almost half of the primary care physicians chose the inaccurate serology rather than the more accurate stool antigen or urea breath tests that detect active infection.[7]

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In this review we focus on updating internists and primary care physicians in *H. pylori* management, because these are the physicians most likely to encounter *H. pylori* relatively frequently, but who may not be aware of the changing prevalence of antibiotic resistance, the plethora of diagnostics tests available, and the recently updated guidelines on managing *H. pylori* infections.

CLINICAL SIGNIFICANCE

- *Helicobacter pylori* infection remains a common clinical issue for internists and primary care physicians.
- *H. pylori* increases the risk of peptic ulcer disease and gastric cancer and is also etiologically linked to idiopathic "functional" dyspepsia, gastric mucosal-associated lymphoid tissue lymphoma, unexplained iron-deficiency anemia, and idiopathic thrombocytopenic purpura.
- Antibiotic resistance is increasingly common among *H. pylori* strains. Recent guidelines support 14-day quadruple therapies over the prior standard of clarithromycin-based triple therapy.

EPIDEMIOLOGY

H. pylori has a prevalence of over 50% globally, with especially high rates in Africa, Central America, Central Asia, and Eastern Europe.[8] In contrast, it is slowly declining in much of the developed world; Hooi et al[8] estimate the prevalence of *H. pylori* infection in the United States to be around 35%. In North America, *H. pylori* is most prevalent among African Americans, Hispanic Americans, Native Americans, Alaskan natives, and in patients with lower socioeconomic status.[9-13] In developed countries such as the United States, it is much more common in the elderly, due to a birth cohort effect of aging from a time when *H. pylori* was much more prevalent.

CLINICAL IMPACT

Since its discovery by Drs. Barry Marshall and Robin Warren, *H. pylori* has been implicated in a number of gastrointestinal conditions, including peptic ulcer disease, gastritis, and gastric malignancies.[1,14]

In patients with gastric mucosa-associated lymphoid tissue lymphoma, eradication of *H. pylori* induces complete remission of this malignancy in most cases.[15] Eradicating *H. pylori* also helps prevent gastric carcinoma, by 30%-50%, according to a recent meta-analysis of randomized clinical trials.[16] Studies have also investigated the relationship between autoimmune gastritis and *H. pylori*, where the treatment of *H. pylori* has resulted in a decrease in the levels of antigastric antibodies.[17] In adults with immune thrombocytopenic purpura, platelet counts tend to increase after eradication of *H. pylori*,[18] leading to a recommendation from the American Society of Hematology to screen for and treat *H. pylori* in adults who test positive.[19]

Certain other extragastric diseases may also be weakly associated with *H. pylori* infections; such as rosacea, chronic idiopathic urticaria, psoriasis, bronchiectasis, chronic obstructive pulmonary disease, Graves disease, diabetes,[20] and possibly, hepatic encephalopathy in patients with cirrhosis.[21]

While there is overwhelming evidence that *H. pylori* is a definite cause of serious gastroduodenal disease, there may also be potential benefits of *H. pylori* colonization. For example, an inverse relationship has been found between *H. pylori* and eosinophilic esophagitis, as well as with Barrett's esophagus and with esophageal adenocarcinoma.[22-24]

DIAGNOSIS

Indications for Testing

H. pylori infection should be sought in patients with history of, or active, peptic ulcer disease, those with a low-grade gastric mucosa-associated lymphoid tissue lymphoma, and in the evaluation of dyspeptic symptoms.[2]

A "test-and-treat strategy" has long been advocated for detecting and eradicating *H. pylori* in patients with dyspepsia with low gastric cancer risk.[3] The most recent version of this strategy targets patients younger than 60 years with chronic or frequently recurring epigastric pain or discomfort in the absence of alarm symptoms, such as unexplained weight loss, progressive dysphagia, odynophagia, recurrent vomiting, family history of gastrointestinal cancer, and iron deficiency anemia.[25] Moreover, if a patient with dyspepsia undergoes endoscopy, *H. pylori* presence should be evaluated in gastric biopsies, with the intention of treating if present.[25] A suitable algorithm for internists is shown in **Figure 1**. It is not recommended to test and treat patients for *H. pylori* who have been diagnosed with gastroesophageal reflux disease, or in investigating those with typical retrosternal heartburn symptoms, because *H. pylori* is not implicated as an etiological factor in gastroesophageal reflux disease.[2]

Some evidence supports *H. pylori* testing in patients initiating chronic nonsteroidal anti-inflammatory drugs or aspirin therapy because *H. pylori* is synergistic with these medications in causing peptic ulcer disease and its complications.[2,3] Furthermore, testing is advisable in patients with unexplained iron deficiency anemia and adults with immune thrombocytopenic purpura.[3]

Diagnostic Tests

Internists and primary care physicians can easily detect the presence of *H. pylori* via noninvasive testing: serology, urea breath testing, and stool antigen detection (**Figure 2**) Serologic testing is widely available but is no longer recommended due to its relatively low sensitivity and high false-positive rates when the background prevalence is low (as it is in the United States).[3] In addition, serology can remain positive long after successful eradication due to antibody persistence. In contrast, the urea breath and stool tests detect only