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The Helicobacter pylori Story: Peptic Ulcer, Intestinal Metaplasia and Gastric Cancer

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Abstract

The description of Helicobacter pylori (HP) in 1983 has spawned an entirely new body of medical literature. We can now state that HP causes most cases of histologic gastritis, is etiologic in most patients with peptic ulcers (although acid is also necessary), and is a predisposing factor in the development of gastric malignancy. Although some have suggested that HP is responsible for non-ulcer dyspepsia, this has not been borne out in studies available at the present time.

HP colonization of the stomach does not appear to be a new phenomenon. Descriptions of bacteria in the gastric mucosa of animals and humans date back approximately 100 years. The natural habitat of HP is the human stomach. The method of HP transmission is not clearly defined, but circumstantial evidence is consistent with fecal-oral transmission. Transmission appears to occur primarily during childhood and is increased with lower socioeconomic status and crowded living conditions during childhood.

Histologic gastritis has long been recognized to be a common finding in the normal population, and its presence is closely paralleled by the presence of HP. The prevalence of HP and gastritis in asymptomatic subjects from the U.S. and Europe increases with age, rising from about 10% in the 20's to about 50% in the 50's60's. In contrast, HP and histologic gastritis occur at an earlier age and with much greater frequency in developing countries; perhaps 80% of people in these areas are infected by the end of childhood. Smoking, alcohol, and gender do not appear to influence HP prevalence.

Helicobacter pylori and Gastroduodenal Disease

HP and histologic gastritis have a strong association with peptic ulcer disease. Approximately 90% to 100% of patients with duodenal ulcers and 70% to 90% of patients with gastric ulcers have HP. A clear-cut pathogenetic mechanism is not available to explain how HP causes gastric and duodenal ulcers. However, multiple prospective treatment trials indicate that HP eradication prevents recurrent peptic ulcers in almost all cases. In addition, treatment for HP also may lead to more rapid ulcer healing.

NSAID's appear to cause ulcers by a mechanism independent of HP and are the most common cause of ulcers in HPnegative patients. At present, we can view HP, NSAID'S, and acid as the 3 primary factors in peptic ulcer disease. Acid must be present for the development of ulcers due to HP or NSAID'S, but acid alone generally does not cause an ulcer unless there is hypersecretory condition such as ZollingerEllison syndrome.

Chronic histologic gastritis and HP are commonly associated with gastric adenocarcinoma, postulated to occur via a sequence of atrophic gastritis to intestinal metaplasia to dysplasia to frank carcinoma. Prospective case control studies showed significant increases in the risk of gastric cancer with HP infection. Since the vast majority of patients with HP infection around the world never develop gastric cancer, other specific host, environmental, and/or HP factors must be crucial in the development of gastric cancer. HP also is associated with rare gastric low-grade MALT (Mucosa-Associated Lymphoid Tissue) lymphomas. Eradication of HP can lead to regression and even resolution of these lymphomas.

Diagnosis

Diagnosis of H. pylori can be divided into 2 categories: those which require endoscopy ("invasive") and those which do not require endoscopy ("non-invasive"). Histologic examination of gastric mucosal biopsy specimens taken at endoscopy still is considered the "gold standard" for diagnosis, but the expense of endoscopy makes these invasive tests less attractive for the widespread diagnosis of H. pylori infection. Thus, there has been great interest in the development of non-endoscopic tests which are less expensive but still have acceptable diagnostic yields.

Endoscopic Tests

The presence of a duodenal ulcer at endoscopy has a positive predictive value and specificity of 90% for the diagnosis of H. pylori. Since no other diagnostic test has a significantly better yield, some authors have suggested that the presence of a duodenal ulcer alone is diagnostic of H. pylori infection and no other diagnostic tests need be done prior to initiating therapy. This is a defensible practice in patients with uncomplicated ulcers. However, patients with complicated duodenal ulcers (e.g., bleeding, perforation) appear to have significantly lower rates of H. pylori infection and, thus, H. pylori infection must be documented in this group of patients.

Endoscopic biopsy and histologic examination is the "gold standard" for diagnosis. The organisms are well seen with routine hematoxylin & eosin staining, although the bacteria are more easily identified with special stains (e.g., Giemsa, silver stain, Genta stain). Rapid urease tests (e.g., CLOtest) for biopsy specimens are also available. These tests contain urea and a pH indicator and rely on the potent urease activity of H. pylori. If H. pylori (and therefore urease activity) is present in the biopsy specimen, urea is broken down to ammonia and carbon dioxide, leading to an elevation in pH and a change in color due to the pH indicator in the test. Culture of biopsy specimens is generally not used outside of research settings because it requires special interest or expertise to achieve acceptably high sensitivity. In addition, diagnosis requires 2-5 days. The major potential utility of culture may be to determine antibiotic sensitivities in patients who fail to respond to antibiotic therapy.

Non-Endoscopic Tests

Two categories of non-invasive tests are used: blood tests for IgG antibodies to H. pylori and urea breath tests.

A variety of commercially-available tests measure IgG antibodies to H. pylori. Rapid, qualitative, in-office tests are inexpensive (about $15), rapid (about 10 minutes), and provide relatively good diagnostic yield (sensitivities and specificities about 80-90%). Alternatively, blood can be sent off to a local laboratory for a quantitative ELISA test, although the cost is much higher (perhaps in the range of $50-$100). These tests have similar sensitivities and specificities-in the range of 75-95%. Whole blood tests are now available which require just a finger stick to obtain a blood sample; the sensitivities of these tests are slightly less than the sensitivities of serum tests. Serologic tests have an increased rate of false positives in elderly patients, and they remain positive for years after successful treatment of H. pylori infection (although titers do decline significantly over 6-12 months). Thus, they are useful as an initial screening test, but they are not used to determine response to therapy.

The urea breath test involves ingestion by the patient of urea labeled with C-13 or C-14. If H. pylori is present, then the urea is broken down to ammonia and carbon dioxide; the carbon dioxide is labeled with C-13 or C-14. Thirty minutes later the patient provides a breath sample (they expire into a bag or tube) and the breath sample is examined for evidence of labeled carbon. A mass spectrometer is used to measure C-13 and a scintillation counter is used to measure C-14. The urea breath test has a sensitivity and specificity of 95%. Examination to confirm eradication is routinely performed at least 4 weeks after completion of therapy, whether endoscopy or a breath test is used. In addition, patients must not be taking bismuth compounds, antibiotics, or proton pump inhibitors (e.g., omeprazole, lansoprazole) during this period in order to avoid suppression of the organism and falsenegative results.

In summary, to diagnose H. pylori, if endoscopy is not being performed, an antibody test is probably the test of choice, based on ease and cost. The urea breath test is a more accurate test, but because of the greater time required (30 minutes) and greater cost ($60-200), it probably will not supplant serology as the standard initial diagnostic test for H. pylori. However, the urea breath test is the test of choice to document eradication of H. pylori after treatment.

Treatment

In the past we treated ulcer disease by treating the acid. Suppression of acid clearly led to healing of ulcers and prevention of recurrent ulcers. However, it makes more sense to treat the primary underlying causes of ulcers rather than to require long term acid suppression via maintenance medical therapy or acid-lowering surgical procedures. Approximately 3/4 of patients with an ulcer will have a recurrence within a year. By reducing acid with maintenance antisecretory therapy (e.g., H2-receptor antagonist) this number can be reduced to 2025%. However, by eradicating H. pylori we can reduce ulcer recurrence to approximately < 10%. We now know that if our patients are cured of their H. pylori infection and they avoid NSAID ingestion, they rarely will develop an ulcer.

A variety of agents are effective against HP in vitro, but the results of singleagent treatment in vivo are disappointing. Therefore, combination therapies are used in an attempt to increase rates of HP eradication. Triple therapy with bismuth, metronidazole, and tetracycline is the original standard therapy (e.g., 2-week course of bismuth subsalicylate 2

tablets qid, metronidazole 250 mg qid, and tetracycline 500 mg qid). In addition, an antisecretory medication is added (H2-receptor antagonist or proton pump inhibitor) to hasten pain relief and improve the eradication rate, making it really quadruple therapy. Eradication rates worldwide approach 90%; in the U.S. bismuth subsalicylate triple therapy provides approximately 80% rate of eradication. The major concern with triple therapy is patient compliance, since 17-18 pills are required daily for 2 weeks.

Due to concerns over complex bismuth-based triple therapies, investigators have been seeking simpler alternate regimens. Dual therapies were popular initially. Use of the proton pump inhibitor omeprazole plus amoxicillin was at first reported to give good results, but subsequent studies revealed eradication rates of 50% or less in the U.S. Omeprazole plus clarithromycin dual therapy gave more uniform cure rates (in the range of 65-75%). These dual therapy cure rates are too low for these regimens to be recommended. However, by adding an inexpensive antibiotic (triple therapy), efficacy can be markedly increased and cost can be lessened (because clarithromycin is used only twice a day and the therapy is sometimes given for less than 2 weeks). Twice daily triple therapy with omeprazole 20mg bid or lansoprazole 30mg bid, clarithromycin 500mg bid, and either amoxicillin lg bid or metronidazole 500mg bid has shown rates of eradication around 80-95%. Although European studies suggest good rates of cure when given for 1 week, eradication rates appear to be lower with 1 week of therapy in the U.S. I suggest 2 weeks of therapy, although 10 days may also be acceptable.

A new agent, ranitidine bismuth citrate (RBC) has also been approved by the FDA-in combination with clarithromycin as a 2-week dual therapy. This gives perprotocol eradication rates in U.S. trials of about 80%. Again, by adding another inexpensive antibiotic (e.g., amoxicillin), eradication rates can be increased and costs lessened. Twice-daily RBC triple therapy with RBC 400 mg, clarithromycin 500 mg, and amoxicillin 1 g can achieve an eradication rate of 90% or better. As mentioned, I do not use the approved dual therapies alone, but rather add another antibiotic to give triple therapy.

At the present time peptic ulcers and low grade MALT lymphomas are the only definite indications for HP treatment. An NIH Consensus Conference in February, 1994 suggested that all patients with ulcers and HP infection-whether presenting for the first time or with a recurrence-should receive therapy to eradicate HP. Patients with a history of ulcers on maintenance therapy or with a history of complicated or refractory ulcers should also be tested for H. pylori (e.g., serologic test) and, if positive, should be treated. Many also suggest that patients presenting with dyspepsia (without alarm symptoms) should have inexpensive antibody testing performed, and, if positive for H. pylori, they should receive H. pylori therapy. Published models suggest that this will be cost-effective, even if only a minority of patients have resolution of their symptoms without needing to undergo more expensive evaluations such as endoscopy. We believe that documentation of HP eradication is required after treatment only in patients with complicated ulcers. Assessment in others can be done if symptoms recur. The long-term rate of reinfection appears to be very low, perhaps 0.3-0.5% per year.