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A New Bacterium, H. pylori, in Gastric Diseases and Cancer

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Abstract

Introduction

After a decade of study, Helicobacter pylori has gained acceptance as an important factor in the etiology of peptic ulcer disease, and perhaps even with chronic gastritis and gastric cancer. In the early 20th century, the pathogenesis of the disorder was believed to be related to stress and dietary factors. Later the concept arose that the development of peptic ulcer disease was caused by injurious effects such as gastric acid; hence the wide-spread use of acid-supressive therapy. Despite these highly effective therapeutic agents, there is still a high recurrent rate of peptic ulcer (60-80% over one year), even after complete healing. It is now known that patients with peptic ulcer disease have a statistically significant increase in the prevalence of H. pylori infection when compared with age-matched controls. More than 90% of patients with duodenal ulcer and 80% of those with gastric ulcers harbor the organism. With this new development, data from many prospective blinded trials have shown that eradication of H. pylori leads to clinical cure of ulcer disease.

In February 1994, the National Institute of Health released a consensus statement outlining the role and treatment of H. pylori in peptic disease. Many questions still remain to be answered regarding the mechanisms underlying H. pylori associated disease, including when and how to carry out the diagnosis and treatment of this new pathogen.

Epidemiology

The epidemiology of H. pylori is now well understood. In Western countries, H. pylori associated gastritis ultimately causes peptic ulceration in about 30% of infected persons. There is increased prevalence with advancing age; over 50% of asymptomatic subjects over age 60 years show evidence of H. pylori infection. Earlier and hispanic), socioeconomic deprivation, and residence in custodial institutions. In underdeveloped parts of the world, the prevalence of H. pylori colonization is nearly 80% by age 30.

Mode of Transmission

Currently, it is thought that person-to-person spread is the most likely form of transmission of H. pylori. This concept is supported by evidence of familial clustering, and a higher than expected prevalence in residents of custodial institutions and nursing homes. Person-to-person transmission by endoscopy has been shown, and gastroenterologists

have more than twice the expected prevalence of infection. H. pylori can also be cultured from the stools of most infected persons. This lends evidence that spread of fecal oral contact with infected persons is likely. In addition, polymerase chain reaction can detect H. pylori in dental plaque from 30% of persons with gastric infection. This may represent contamination from gastric reflux or an actual reservoir of the organism in the oro-phamyx. Although the organism has not been isolated from food, water, or animals that humans typically come in contact with, one study showed that the prevalence of infection was associated with drinking water.

H. pylori and Peptic Disease

The causal relationship between H. pylori and chronic superficial gastritis is well established. The evidence for the association is based on:

1. virtually all H. pylori-positive patients demonstrate antral gastritis,
2. eradication of H.pylori infection results in resolution of gastritis and
3. the lesion of chronic superficial gastritis has been reproduced following intragastric administration of the organism in animal models and in human volunteers.

A causal relationship between H. pylori and peptic ulcer disease is more difficult to establish, in part because of the lack of an animal model, and because only a small proportion of individuals harboring the organism develop ulceration. However, nearly all patients with duodenal ulcer have H. pylori gastritis. Thus, infection with the organism may be a prerequisite for the occurrence of almost all duodenal ulcers in the absence of other precipitating factors such as nonsteroidal anti-inflammatory drug (NSAID) use or Zollinger-Ellison Syndrome. The association between H. pylori infection and gastric ulcer is only slightly less strong, in that 80% of patients with non-NSAID-induced gastric ulcers are infected. Nevertheless, it is important to note that the majority of H. pylori-infected individuals do not develop duodenal or gastric ulcers. Perhaps host characteristics, strain variability, or other factors play a role in the pathogenesis of peptic ulcer disease.

The strongest evidence for the pathogenic role of H. pylori in peptic ulcer disease is the marked decrease in recurrence rate following the eradication of infection. The prevention of recurrence following H. pylori eradication is less well documentated for gastric ulcer than that for duodenal ulcer, but the available data suggest similar efficacy.

There is no convincing evidence for an association of H. pylori infection with non-ulcer dyspepsia. The prevalence of H. pylori infection is no higher in patients with non-ulcer dyspepsia than that in the general population. Although a subset of patients with non-ulcer dyspepsia may exist in whom symptoms are related to the presence of H. pylori, there are no data to demonstrate this association.

H. pylori and Gastric Cancer

The incidence of gastric adenocarcinoma has declined in the United States since the 1930's. At that time, it was the most common cancer but now it ranks about ninth. The current incidence is only 6 per 100,000 persons per year, a decline from 50 per 100,000 in 1930. Worldwide, however, gastric cancer is still the second most common cancer after lung

cancer, and is particularly high in areas such as Brazil, Colombia, Korea, China and Japan. H. pylori infection affects more than half of the population in these countries. In an extensive review of gastric cancer and H. pylori, the Eurogast Study Group determined that the presence of H. pylori confers an approximately six fold risk of gastric cancer, accounting for about half of all gastric cancers. Supposedly, chronic gastritis leads to intestinal metaplasia (atrophic gastritis) which then undergoes malignant change. Recent data presented in abstract form suggest that eradication of H. pylori heals this process and removes a key factor in the chain of events. However, there are also some clear examples of disparity in the epidemiology of the two diseases. Gastric cancer is more common in men than in women, whereas the rates of H. pylori infection are not different between the sexes. Some populations are also reported to have a high rate of H. pylori infection but low rates of gastric cancer. These disparities indicate that factors other than H. pylori infection are also important in the risk of gastric cancer.

Geographic studies of H. pylori and gastric cancer incidence reveal striking epidemiologic parallels between the two. Internationally, H. pylori infection, like gastric cancer of the intestinal type, has foci of high prevalence, usually in countries of lower socioeconomic development. In high-risk cancer regions, infection is also acquired early in childhood; in countries with low cancer rates, pediatric infection is unusual. Parallels between H. pylori and cancer incidence are maintained within national borders as well. Forman el al. found a significant correlation between H. pylori seroprevalence and gastric cancer rates among 49 Chinese counties. H. pylori prevalence has also declined over time concomitantly with the decrease of incidence of cancer. In a study performed on banked serum, infection prevalence correlated inversely with year of birth. Because infection is presumed to precede cancer by many years, however, these simultaneous decrease must be interpreted with caution. Clearly, parallel geographic and temporal trends may reflect a factor (e.g. socioeconomic status) influencing both diseases rather than a causal association.

Three prospective case-control studies in distinct populations have been shown remarkable concordant evidence that H. pylori infection increases risk for later development of gastric malignancy. The study population, from Great Britain, California, and Hawaii, are all cohorts that have been followed over many years for clinical outcome, including cancer. Despite the ethnic diversity, cancer subjects in the three studies had similarly high risk of prior infection with H. pylori than did controls. This increased risk was restricted to adenocarcinoma of the antrum, body or fundus; tumors of the cardia and gastroesophageal junction were not linked to infection. From this work, a crude attribute risk between 35 and 89% can be estimated; in other words, between 35 and 89% of cancer would not occur if H. pylori did not exist. Implicit in the estimate of attributable risk, however, is the still unproven assumption of causality.

In addition to gastric adenocarcinoma, gastric lymphomas have also been linked to H. pylori. Retrospective biopsy studies show that 90% of such lymphomas are associated with H. pylori. In H: pylori associated gastritis, lymphoid follicles are also seen but they largely regress after effective therapy for the infection. Lymphoma should be suspected whenever chronic inflammation fails to regress after eradication of H. pylori.

Diagnosis

There are now numerous methods which have been validated to diagnose patients with H. pylori infection. Invasive tests include endoscopy with gastric biopsy and histologic demonstration of organisms, biopsy with direct detection of urease activity in the tissue specimen, and biopsy with culture of the H. pylori organism. Although culturing the organism is traditionally considered the "gold standard" for diagnosis of many infectious agents, it is the least sensitive diagnostic test (70-80% accuracy). Both histologic demonstration of the organism by Giemsa or Warthin-Starry stains and urease testing have sensitivities and specificities above 90%.

Excellent diagnostic sensitivities and specificities (over 95%) are also obtained with noninvasive tests for the initial diagnosis of H. pylori infection. These include serology for IgG to H. pylori antigens and breath tests of urease activity. A number of highly accurate serologic kits for diagnosis of H. pylori infection are available. Labeled urea tests have had restricted availability as research tools in the past, but commercial assays will be available in the near future.

Treatment

Therapy for H. pylori poses several unique challenges. The organism resides under a mucus gel layer in the highly acidic milieu of the stomach, where rapid removal of ingested antimicrobials may occur. A problem in selection of a therapeutic regimen has been the lack of suitable animal model. For these reasons, much of the available information concerning choice of antimicrobial agents is based on small empiric trials in humans. Multiple agents have been studied in various combinations which include metronidazole, tetracycline, amoxicillin, erythromycin, bismuth compounds, H2 -receptor antagonists, and proton-pump inhibitors. Consideration of the therapeutic options must also take into account efficacy, compliance, side effects and cost. A triple antimicrobial regimen containing bismuth subsalicylate, tetracycline, and metronidazole has been studied extensively and can yield eradication rates of over 90%. Substitution of amoxicillin for tetracycline or metronidazole lowers efficacy only slightly (>80%), although variable eradication rates of over 80% have also been reported with the double combination of omeprazole and amoxicillin. Omeprazole should be given at least twice daily, and the two agents begun at the same time because immediate pretreatment with omeprazole lowers the efficacy of the omeprazole-amoxicillin combination. Two or three-drug regimens should last two weeks.

Resistance to antimicrobials, in particular to metronidazole, is an important problem and a cause for treatment failure in some studies. Resistance to metronidazole varies worldwide, with the highest rates (45-50%) in underdeveloped countries. Application of currently available one-drug regimen has led to enhanced antimicrobial resistance and thus is strongly discouraged. The wide spread application of antimicrobial regimens to treat infection may magnify the problem of drug resistance.

Finally, which H. pylori-infected patients should be treated? Guidelines have now been established in a consensus statement from the NIH. All patients with gastric or duodenal ulcers who are infected with H. pylori should be treated with antimicrobials regardless of

whether they are suffering from the initial presentation of the disease or from recurrence. Peptic ulcer patients who are infected with H. pylori and are undergoing maintenance treatment with antisecretory agents should also be treated for the infection. The presence of NSAID should not alter the antimicrobial regimen. However, in the asymptomatic H. pylori-infected patients without ulcers, the data are not sufficient to support prophylactic antimicrobial therapy to prevent ulcer disease in the future, or to reduce the liklihood of developing gastric neoplasia. Also, no convincing data exist to support routing treatment of patients with non-ulcer dyspepsia who are H. pylori-infected. Thus, at the present time there is no reason to consider routine detection or treatment of H. pylori infection in the absence of ulcers. Carefully controlled prospective studies are needed to assess the benefits of treating non-ulcer dyspepsia with H. pylori infection.

Bleeding is the complication of peptic ulcer disease with the highest mortality rate and therefore, demands aggressive therapy. The available data suggest that after these ulcers heal, the likelihood of recurrence of bleeding is significantly reduced by maintenance antisecretory therapy. Preliminary studies indicate that eradication of H. pylori infection may be equally efficient in preventing the recurrence of ulcer bleeding. Until these studies can be confirmed, maintenance antisecretory therapy may be prudent in such patients even after H. pylori eradication in view of the high risks associated with re-bleeding.