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**Helicobacter Pylori**

**History**

Spiral bacteria have been found in the human stomach since 1906. They were believed to lead to chronic inflammation and gastritis, but this theory was abandoned in favor of chronic stress, leading to acid and pepsin hypesecretion, as an explanation for the pathogenesis of chronic peptic ulcer disease. Treatment focuses on hospitalization, bed rest, and prescription of special bland foods. Antacids and medications that block acid production become the standard of therapy. Despite this treatment, there is a high recurrence of ulcers. However, in 1982 Warren and Marshall in Australia revived interest in the hypothesis that peptic ulcer disease might be caused by an infection when they cured a patient with chronic peptic ulcer disease by treatment with tetracycline. Subsequently, they isolated the putative causative organism, which was originally called *Campylobacter pyloridis* but was later named Helicobacter pylori (H. pylori). The organism was linked to peptic ulcer disease and chronic gastritis, and they demonstrated that these diseases could be treated successfully with antibiotics. In response to skepticism about the importance of H. pylori as the etiologic agent of gastritis, Marshall had himself gastroscoped to prove that his stomach was normal, then ingested H. pylori after neutralizing his stomach acid with histamine blockers. After about 7 days, he developed epigastric discomfort and vomiting. Repeat gastroscopy showed that the organism had colonized the stomach and led to acute inflammation. The organism and the pathology could be cleared with antibiotic therapy. This experiment was repeated subsequently by another investigator but the antibiotics failed to clear the H. pylori, and gastritis persisted. These self-experiments were followed with hundreds of studies of the association of H. pylori and gastric pathology. The studies have clearly and consistently shown a strong association between infections with H. pylori and dyspepsia, peptic ulcer disease involving both gastric and duodenal ulcers, hypertrophic gastritis, gastric cancer, and gastric lymphoma. As a result of these data, a consensus conference sponsored by the NIH in 1994 concluded that H. pylori infection was a major cause of peptic ulcer disease and recommended that antibiotic therapy become the mainstay of treatment.

**Prevalence**

*H. pylori* is one of the most common infections that affects humans. Although *H. pylori* was identified as recently as in 1983, numerous studies reveal that it is encountered worldwide. It is estimated that half or more of the world's population is infected. Substantial differences in the prevalence of *H. pylori* infection have been observed between countries. These differences conform to two major patterns that differ in developed and developing countries. The general trend of *H. pylori* prevalence in developed countries is slow increases during childhood, which continue through adolescence and early adulthood; in many developed countries there is an abrupt increase around 50-60 years of age. In developing countries, *H. pylori* prevalence increases more rapidly during childhood and most adolescents and adults are infected. Thus, differences in *H. pylori* prevalence between developed and developing countries are greater at younger ages and get smaller at older ages. Figure 1 shows *H. pylori* prevalence in developed and developing countries across different age groups. Although the overall prevalence is generally lower in developed countries, high prevalences, approaching that of developing counties, have been observed within some subgroups in developed countries. Differences in prevalence within populations are due to a variety of factors, primarily relating to socioeconomic status and geographic origin.

Figure 1. Prevalence of *Helicobacter pylori* infection according to data from developing countries and developed countries.

**Transmission**

Despite the large volume of research on *Helicobacter pylori,* the mode of transmission is still not well understood. Although this infection appears to be transmitted directly from person-to-person, the precise pathway from one person to another is controversial and it is not known if other modes of transmission are involved. Varying degrees of evidence suggesting oral-oral, fecal-oral, gastro-oral, waterborne and zoonotic transmission have been reported. Evidence for various transmission pathways is presented in table 1.

Table 1. Evidence for *H. pylori* transmission pathways

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Person-to-person transmission

Clustering in families and group residences.

Association with residential crowding.

Association with high birth order and narrow birth spacing.

Isolation from human feces and dental plaque.

Detection in human feces, saliva and dental plaque by polymerase chain reaction.

Waterborne transmission

Survival in laboratory aquatic environments.

Detection by polymerase chain reaction in water samples from Colombia, Peru And Sweden.

Association with drinking water source in Andean countries.

Association with raw vegetable consumption in Andean countries.

Association with swimming in rivers and swimming pools in Andean countries.

Zoonotic transmission

Successful experimental infection of monkeys, mice, cats, germ-free pigs, germ-free dogs,

Observation of natural infection in research monkeys and cats.

Observation of human infection by animal *Helicobacter* species.

Increased prevalence linked to contact with sheep.

Iatorgenic transmission

Signs and symptoms of acute infection observed among gastroscopy patients.

Detection of viable *H. pylori* in manually disinfected gastrofiberscopes.

Risk of reinfection increased by endoscopy following antibiotic therapy for *H. pylori.*

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**Factors associated with increased prevalence of *H. pylori* infection**

Several factors have been found to influence the prevalence of *H. pylori* infection*.* Evidence regarding determinants of *H. pylori* prevalenceis limited because it comes largely from small studies with inadequate control of confounding. Implicated factors include age, ethnicity, socioeconomic status indicators, household crowding indicators, and migration from high prevalence regions. Other factors also include having *H. pylori*-infected parents, the number of children in the home, high birth order, and institutional residence. Some evidence suggests that poor nutritional status, drinking water source, consumption of raw vegetables and swimming in rivers or streams may influence *H. pylori* prevalence.

**Age**

Studies show that the prevalence of *H. pylori* increases with age. This has been observed in studies using wide age ranges for age-specific prevalence. However, this observation has not held in some studies that observe narrow age intervals in childhood. In fact, decreases in the prevalence over narrow ages in childhood have been noted. It is not known whether such decreases in prevalence reflect a peak occurrence during early childhood and subsequent resistance to persistent infection in some populations. It is possible that changes in host characteristics or exposure to factors such as antibiotics may influence susceptibility to the persistence of the infection.

The observed increases in *H. pylori* prevalence with age beyond childhood do not seem to result from an increased risk of *H. pylori* acquisition with age. In fact, in many populations, the prevalence does not continue to increase throughout adulthood; several studies have reported a leveling of increases in prevalence at older ages (fig 1). Birth cohort analyses in developed countries suggest a cohort effect that reflects higher incidence in childhood in previous decades and declining age-specific prevalence in more recent cohorts. Changes in sanitation may explain the cohort effect observed in developed countries, given that sanitary conditions have improved during the last few decades while *H. pylori* prevalence has apparently declined.

Two studies have shown an association between current prevalence of *H. pylori* infection and exposure to factors during childhood. For example, Malaty et al. observed an inverse relation between adult prevalence of *H. pylori* infection and socioeconomic status during childhood. Webb et al. observed that childhood living conditions predicted *H. pylori* prevalence in adults*.* These findings, along with the findings from the birth cohort analyses and patterns of age-specific prevalence, suggest that *H. pylori* is most often acquired in childhood. However, the peak age at which *H. pylori* is acquired is unknown. A recent national serosurvey conducted in Mexico showed that 25% of children were infected by the age of 4 years; the sharpest increase (6%) was observed between age 3 and age 4. The rate of increase in prevalence decreased to almost 0% by the age of 60.

**Ethnicity**

Several epidemiological studies have explored patterns of *H. pylori* prevalence by ethnicity. In the U.S., analysis of data from the National Health and Nutrition Examination Survey III (NHANES III), conducted during 1988-1991, among children between the ages of 6 and 19 years old, showed that the prevalence of *H. pylori* infection differed by ethnic group. The prevalence of *H. pylori* infection was 17% among non-Hispanic whites, 40% among non-Hispanic blacks and 42% among Mexican-Americans. In another study of preschool children (5-8 years old) in Ulm, a city in the South of Germany, the prevalence was 6% among German children and 45% among Turkish children. In a study of three different ethnicities in a group of individuals aged 0 to 60 years in Singapore, the prevalence in children 20 years or less was 23% among Indians, 17% among Chinese and 16% among Malays. In a study of children under 17 years of age who were born in Malaysia, the prevalence was 18% among Indians, 10% among Chinese and 7% among Malays.

Various investigators have observed that ethnic groups with higher prevalence often originate from high prevalence geographic regions. In a study of 466 Belgian children aged 2-14 years, the prevalence was 6% among Belgian children, 20% among African children, and 19% among Mediterranean children. Moreover, within the same ethnic group, researchers have observed an association between increased prevalence and birth in a high prevalence region. For example, among Mexican American children participating in the United States National Health and Nutrition Examination Survey (NHANES III), the prevalence was 37% among those who were born in the U.S., and 58% among those who were born outside of the U.S.

It is not certain what an association between *H. pylori* and ethnicity reflects. Beyond the possibility of differences in genetically determined susceptibility to infection, ethnic differences in prevalence may be related to social and economic factors, such as poverty, crowding, and education, as well as originating in a geographic region that has a high prevalence of infection or being born to immigrants from such a region. In general, ethnicity is a marker of a variety of lifestyle exposures, such as differences in standards of living or sanitation practices.

**Socioeconomic status**

Socioeconomic status (SES) is another major determinant of *H. pylori* infection. Most studies that have evaluated the relationship between the prevalence of *H. pylori* infection and the childhood level of SES show an inverse relationship. On the other hand, a few studies that have evaluated the relationship between *H. pylori* prevalence and current SES in adults have shown an absence of association. As an example, in a serosurvey in the Houston metropolitan area among 483 healthy volunteers (15-80 years), the data showed an absence of association between the current level of SES and the prevalence of *H. pylori* infection. Another study conducted in Russia showed an absence of association between *H. pylori* prevalence in adults and education level, household income, type of dwelling and total number of rooms, although an association was observed between *H. pylori* prevalence and a crowding index. If SES during childhood is an important determinant of persistent infection, adult SES may be unassociated with the prevalence of infection in populations in which many individuals have changed their status since childhood or if the individuals in these populations had similar childhood living conditions regardless of SES. It is also possible that effects of socioeconomic factors may be missed if the study populations have limited variation in SES. Further, the relationship between socioeconomic influences and the prevalence of *H. pylori* infection may sometimes be obscured due to the complexity of defining and measuring SES, given that there is no universal method for defining and measuring this variable, which captures a variety of influences such as income, education level, housing conditions, crowding, hygiene, nutritional status and occupational exposures.

Since a number of different measures can be used to indicate socioeconomic status, there has been much debate as to what each indicator actually measures, and how choice of indicator influences the observed pattern of inequalities observed within or between communities. When comparing SES within and across communities, some issues should be considered. Some of these issues may include: the type of indicators; whether or not they interact with each other or with other factors; whether they behave the same way in different communities; and, if not, whether community differences need to be considered in the analysis. So, it is clear that there are many challenges in evaluating SES and in the interpretation of SES measures, especially international studies where sources of incomparability will be increased.

**Detection of *H. pylori* infection.**

Tests for *H. pylori* infection can be divided into two groups: invasive tests and noninvasive tests.

**1. Invasive tests**

The invasive tests are endoscopy-based because they require biopsy samples. These can be further classified into:

*A. Biopsy urease test.*

Biopsies are taken from the antrum and corpus and placed in a gel containing urea and an indicator. Since *H. pylori* is a urease-producing organism, if the patient is infected with the organism, the gel will change color. Using combined results from available *H. pylori* detection methods as a gold standard, where a result is considered to be positive when two or more tests are positive,this test shows moderate to fairly high sensitivity and high specificity prior to antibiotic treatment, with sensitivity in the range of 80% to 90% and specificity in the range of 99% to 100%. The sensitivity and specificity of the test may vary depending on the number of bacteria present in the biopsy specimen, the site where the specimen was taken, the time lapsed before tests are read, and the type of diagnostic kit used.

*B. Histologic examination.*

In this test, biopsy specimens are collected and special stains such as the modified Giemsa or silver stain are added to enable the pathologist to visualize *H. pylori* clearly. Using combined results from available *H. pylori* detection methods as a gold standard, where a result is considered to be positive when two or more tests are positive, reports show that the sensitivity and specificity, under optimal conditions, are around 93% and 98%, respectivley. Factors including where biopsies are taken from the stomach, the number of specimens examined, eradication treatments, biopsy preparation techniques and pathologist expertise may greatly affect the accuracy of this test.

*C. Microbiologic culture.*

A nutrient media such as Brain-Heart agar with horse blood is required to promote the growth of the organism. The cultures are incubated for 3-5 days at room temperature (37C). This test permits determination of antibiotic susceptibilities. It has been argued, if sampling errors are avoided,that culture is the most sensitive biopsy-based technique because it is usually not affected by the bacterial load of the biopsy. Even one organism in the biopsy can multiply to produce a positive result. However, bacteria do not always grow on the plate because of problems related to biopsy handling or laboratory conditions. Using combined results from available *H. pylori* detection methods as a gold standard, where a result is considered to be positive when two or more techniques are positive, the reported sensitivity of culture has ranged from 50-95% and specificity may reach up to 100%.

Since endoscopy is often used in the management of symptomatic patients to determine their disease status, the *H. pylori* status of such patients is often determined by biopsy-based tests. However, performing endoscopy to diagnose *H. pylori* in asymptomatic subjects is not generally recommended. Thus biopsy-based methods are not suited for epidemiologic studies, so reliable noninvasive diagnostic techniques are required.

**2. Noninvasive tests:**

Two noninvasive diagnostic tools, serologic assays and urea breath tests, have been used in epidemiologic studies of children. One newly developed technique, a stool antigen test, is in the process of evaluation. These tests do not require endoscopy for biopsy samples:

*A. Serologic assays.*

These are the simplest and most frequently used tests. They are inexpensive, suitable for testing large numbers of subjects, and require little time. They involve the measurement of specific IgG levels in blood samples. This procedure has high sensitivity and specificity among adults and older children. Using the results of biopsy-based tests as a gold standard, sensitivities and specificities have been reported in the range of 95.8-100% and 91-96.2%, respectively. However, the interpretation of serologic assays is problematic, because exposure to *H. pylori* may not confer an immediate or lasting immunological response. Follow-up of successfully eradicated infections show that IgG levels decline following treatment, often to undetectable levels. Substantial declines in the antibody titer usually takes place the first 3 to 12 months after antibiotic treatment. Thus, positive serology may reflect a current or cleared infection, while negative serology may reflect never having been infected, having been infected in the past, or recently having acquired the infection. Moreover, in very young children, reports show that serological tests results reveal a much lower prevalence of *H. pylori* infection than is indicated by the 13C-urea breath test. Thomas et al. observed that the discrepancy between the 13C-urea breath test and serological tests is most obvious during the first year of life. This reflects a delay in the development of an immune response in infants. These factors may limit the use of this test as a diagnostic tool in very young children.

*B. Urea breath tests.*

Another well-established diagnostic technique is the urea breath test. In this procedure, urea labeled with 13C (a nonradioactive isotope) or 14C (a radioactive isotope) is dissolved in liquid and given to a person to drink. The 14C-urea breath test is not recommended for use in children. The 13CO2/12CO2 isotope ratio in a baseline sample of exhaled breath is compared to that of samples collected 15 to 30 minutes after ingestion. Since *H. pylori* is a urease-producing organism, when the organisms are present in the stomach the urea is metabolized into ammonia and carbon dioxide. The labeled carbon is thus liberated in the form of 13CO2, leading to an increase in the 13CO2/12CO2 isotope ratio over baseline.

Validation studies of the urea breath test, using biopsy-based diagnostic methods as a gold standard, have shown high reported sensitivities and specificities in adults and older children. In adults, validation studies, using biopsy-based methods as a gold standard, have estimated the sensitivity and specificity to be greater than 95%. This procedure has not been validated adequately among infants and very young children.