HELICOBACTER PYLORI:
NEW ANSWERS, NEW QUESTIONS

Medical Grand Rounds

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INTRODUCTION

Helicobacter pylori was brought to the world's attention in 1983 when Warren and Marshall, two Australian investigators, reported spiral organisms in mucosal biopsies of patients with chronic active gastritis (1). First named *Campylobacter* ("curved rod") *pylori*, its name was changed to *Helicobacter pylori* (*H. pylori*) when biochemical and genetic characterization of the organism showed that it was not a member of the Campylobacter genus. Microbiologists, particularly those working in the area of *Campylobacter,* took up the challenge and there was an almost immediate outpouring of scientific papers that confirmed and extended the original observation. The gastroenterology community was slower to accept the hypothesis that a bacterium might be the cause of peptic ulcer disease. Proof was eventually forthcoming and it is now acknowledged that *H. pylori* gastritis is one of the most common human bacterial infectious diseases and is causally linked with gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric B-cell lymphoma. The role of *H. pylori* in non-ulcer dyspepsia is less certain.

H. pylori is a slow-growing, micro-aerophilic, highly motile, Gram-negative spiral organism whose most striking biochemical characteristic is the abundant production of urease. This enzyme may be crucial for initial colonization and is an important indirect marker of the organism's presence as it is the basis of biopsy rapid urease tests, the urea breath test, and as an antigen for serologic detection. *H. pylori* is tropic for gastric epithelium (i.e., stomach and areas of gastric metaplasia outside the stomach). A very small proportion of organisms can be found intracellularly but the significance of this in relation to the inflammatory response and evasion of antimicrobial therapy is yet unclear. *H. pylori* infection elicits robust inflammatory and immune responses which are life-long unless the infection is cured.

EPIDEMIOLOGY

PREVALENCE IN HEALTHY INDIVIDUALS

The prevalence of *H. pylori* in otherwise healthy individuals varies depending upon age and country of origin (Figure 1). In developing countries many children are already infected by age 10 whereas in developed countries, there is a clear age-related increase in prevalence (2-5). In developed countries such as the United States, prevalence may vary among different ethnic groups of similar socioeconomic status (6) (Figure 2). Both environmental and genetic components contribute to these differences.

Environmental Factors

H. pylori infection occurs primarily during childhood; only about 0.3%-0.5% of adults become infected per year (7-9). The major risk factor for infection is the socioeconomic status of the family during childhood (Figure 3), as manifested by such factors as the number of persons in a household, sharing a bed, absence of a fixed hot

Figure 1. Sero-prevalence of H. pylori as a function of age in developing countries (India, Algeria, Saudi Arabia) and developped countries (England, France, Australia). From reference (5).

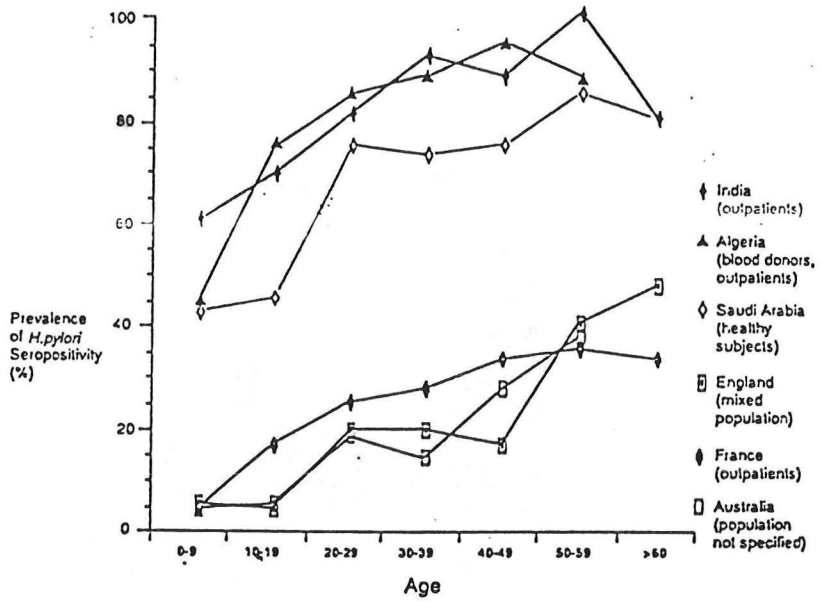


Figure 2. U.S. sero-prevalence of H. pylori as a function of age in asymptomatic Black African-Americans, Hispanics, and Whites. From reference (3).

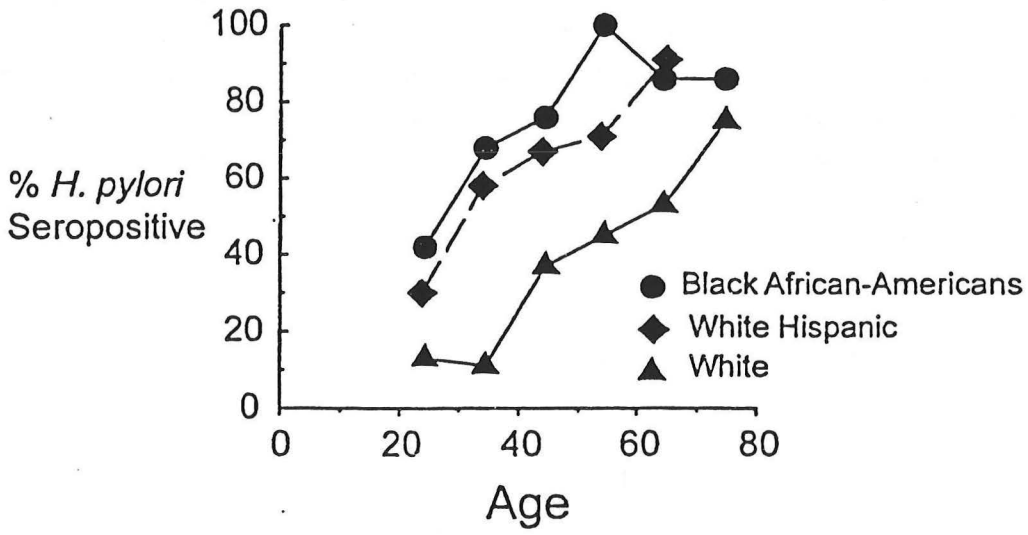
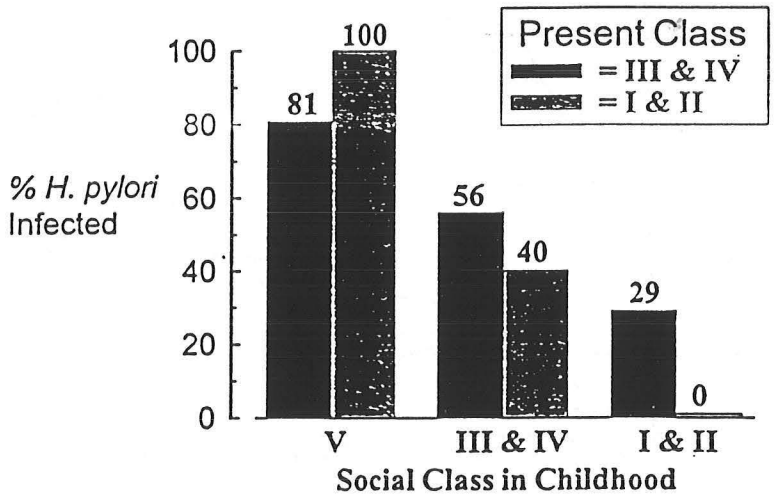


Figure 3. Sero-prevalence of H. pylori as a function of social class during childhood and at the present. Income is highest in Class I and lowest in Class V. From reference (10).



water supply, and poor sanitation (10-15). As the socioeconomic status of individuals and countries has risen, the prevalence in younger generations has declined (16). Thus, the age-related pattern of infection in developed countries (Figure 1) can best be explained by the "cohort effect." As successive generations have been less likely to become infected as children, these cohorts show a lower frequency of infection as adults. Improvement in socioeconomic status among blacks and hispanics in the United States has lagged behind other groups and is one explanation why the overall prevalence of *H. pylori* in these groups is higher (Figure 2). Socioeconomic conditions have improved even more slowly in developing countries, which explains the continuing high rate of infection in young people.

Genetic Factors

Two recent studies lend credence to a genetic predisposition to infection with *H. pylori*. In one study from Belgium, Caucasian children had a significantly lower seroprevalence of *H. pylori* infection than did non-Caucasian children matched for age and socioeconomic status (17). In another, monozygotic twins reared apart or together had a higher rate of concordance of infection than did age-matched dizygotic twins (18).

TRANSMISSION OF INFECTION

Evidence of *H. pylori* has been found in water using the polymerase chain reaction (19) and there is strong epidemiologic evidence of water borne transmission in Peru and Colombia. However, with possibly one exception, the organism has never been cultured from traditional environmental reservoirs such as water, insects, pets, or farm animals. The exception is a colony of domestic cats which has recently been shown to harbor human *H. pylori* (20), although the importance of this observation remains to be determined and a number of epidemiology studies have failed to show a relationship between owning cats and *H. pylori* infection. Thus, the bulk of the data suggests that the organism is likely transmitted from person-to-person. Support for this concept comes from studies of children in institutions of custodial care, where prevalence is higher than expected (21), and from studies of families in which there is at least one child (22-24). Whether an infected child (22) or parent (23) is used as the index case, other family members are substantially more likely to be infected than family members of an uninfected person (Figure 4).

Figure 4. Sero-prevalence of H. pylori in spouses and children of parents who are positive or negative for H. pylori infection. From reference (23).

The means by which *H. pylori* is transmitted among individuals is uncertain and arguments can be made for and against each possibility. The first possibility is fecal-oral transmission. *H. pylori* has been found in stool by PCR (25) and culture (26,27); shedding of bacteria into the stool may be enhanced by diarrhea (26) or drugs which raise gastric pH (28). Unfortunately, culture of *H. pylori* from stool has proven to be extremely difficult and detection by PCR does not ensure the organisms are living. Further evidence against fecal-oral transmission comes from studies in rats infected with *H. felis* (another helicobacter naturally found in cats), where infection could not be transmitted from infected animals to coprophagous uninfected animals (29).

A second possibility is oral-oral transmission, where evidence of *H. pylori* in dental plaque and saliva has been found by culture (30,31) and PCR (32). Evidence against oral-oral transmission is that couples without children have a low prevalence of concordance of *H. pylori* infection (33) and dentists and dental staff are not at increased risk of infection (34).

A third means of transmission is gastro-oral (35). Evidence to support such a model include well-described epidemics of *H. pylori* gastritis in volunteers undergoing gastric intubation experiments (36-38), transmission of infection from one patient to another by inadequately disinfected endoscopes (39), and possibly a higher-than-expected prevalence of *H. pylori* in gastroenterologists, especially those who had not worn gloves in the past (40). One means by which gastro-oral transmission could occur from child to child or child to parent in a natural setting is through contact with the vomitus of an infected child (35). On the other hand, this theory could not explain possible transmission from parent to child. While more work is needed to sort out this aspect of *H. pylori* epidemiology, it appears that any method by which *H. pylori* can obtain access to the stomach can potentially serve as a means of transmission. For prevention of transmission we need better understanding of the most common modes of transmission in children as well as identification of weak links in the transmission chain.

ACUTE INFECTION

Acute infection with *H. pylori* has been observed in several individuals (41-45). In two cases, investigators themselves knowingly ingested a culture of *H. pylori* after endoscopic biopsy had confirmed absence of pre-existing infection (41-43). Both subjects developed a severe neutrophilic gastritis and, in one, fasting gastric pH was above 7.0 from day 8 to day 39 after ingestion. Another individual, a clinical investigator working with gastric juice, developed an illness characterized by epigastric pain and nausea (44). On the fifth day of illness an endoscopic biopsy disclosed a neutrophilic gastritis and culture grew *H. pylori*. Although this individual did not have a baseline endoscopic exam, sero-conversion occurred between day 14 and 74. Fasting gastric pH was above 7.0 on days 14 and 37, but fell to 2.0 on day 74.

The neutrophilic gastritis with transient hypochlorhydria observed in these subjects was reminiscent of cases noted in several research laboratories during the 1970's and 1980's (36,37). In one of these outbreaks, 17 of 37 healthy volunteers participating in acid secretory studies and one patient with Zollinger-Ellison syndrome became rapidly and profoundly hypochlorhydric (36). Nine of the 17 volunteers noted a 1-4 day illness consisting of mild to moderate epigastric pain accompanied by nausea in four and vomiting in two. Biopsies of the gastric body in 12 subjects revealed severe neutrophilic gastritis in each. Short term follow-up showed lessening of the severity of gastritis and return of acid secretion to near baseline levels in 14/17 volunteeers within a mean of four months. Despite an intensive search for an etiologic agent, none was found at the time. Subsequent to this "epidemic" an additional 17 cases occurred bringing to 35 the total number of such cases occurring in this laboratory. Following the recognition of *H. pylori*, the investigators involved reviewed the original biopsy material and found *H. pylori* in 7 of 12 subjects. Additionally, samples of stored serum from before, during, and after hypochlorhydria were tested for IgG and IgM antibodies to *H. pylori* (38). Data from these studies strongly suggest that, in retrospect, these cases of acute gastritis with hypochlorhydria were temporally related to acute infection with *H. pylori*.

VIRULENCE FACTORS

H. pylori possesses a number of factors which allow it to colonize and persist in the stomach and to induce tissue injury (Table 1).

Table 1. Virulence factors possessed by *H. pylori* which promote colonization and induce tissue injury.

Promote Colonization	Induce Tissue Injury
Motility	Lipopolysaccharide (LPS)
Urease	Leukocyte recruitment and activating factors
Induction of hypochlorhydria	Cag A and Vac A proteins
Adherence	Heat shock proteins
NH_4^+/H^+ ATPase	

Colonization Factors

Colonization factors are attributes of an organism which allow it to establish its presence and to persist despite the body's attempts to rid itself of infection. These factors permit *H. pylori* to find its niche in an acidic environment which is inhospitable to virtually every other enteric organism.

Motility

The combination of a spiral shape and monopolar, sheathed flagella serve to move *H. pylori* quickly from the lumen of the stomach, where pH is low, through the mucus layer to an area where pH is near neutral to permit optimal growth. Mutant strains of *H. pylori* which are non-motile will not colonize the gnotobiotic piglet, a well-described animal model for *H. pylori* infection (46). An important component of *H. pylori* flagella, the flagellar hook, has been characterized. Strains with mutations in the *flgE* genes, which code for the flagellar hook, are non-motile (47).

Urease

H. pylori is a more powerful producer of urease than almost any other bacterial species. This nickel-containing hexadimer is essential for colonization, as shown by studies in which a mutant strain of *H. pylori* without urease activity will neither grow *in vitro* at pH below 4 (48) nor colonize the gnotobiotic piglet (49). However, the mechanism of urease's necessity remains unclear. The same study of *in vitro* growth noted above showed that wild-type *H. pylori* is inhibited at pH below 4 if urea is not present in the medium, suggesting that local neutralization of acid by ammonia generated from urea by urease may be important (48). This cannot be the only mechanism, however, since another study found that urease-negative mutants of *H. pylori* could not colonize piglets even when the animals were rendered achlorhydric by omeprazole or the mutant strains were co-inoculated with wild-type strains (50). The latter experiment also excludes the possibility that urease induced hydrolysis of urea provides an essential nitrogen source for protein synthesis. Finally, urease is not essential for adherence. There is no difference in adhesion to gastric epithelial explants between wild-type and urease-negative strains (51).

Induction of Hypochlorhydria

The most crucial time for *H. pylori* to avoid the effects of gastric acid is during the initial stages of infection. It is thus fortuitous that the acute infection is accompanied by transient hypochlorhydria. The mechanism by which the organism accomplishes this feat is unknown. Possible mediators include acid inhibitory proteins, lipopolysaccharide, or mucosal cytokines (see below) (52). It also remains unknown how this effect of *H. pylori* is diminished several weeks after onset of infection. Ironically, failure of acid secretion to return to normal levels might ultimately be harmful to the organism. Not only is *H. pylori*

sensitive to low pH, it is sensitive to high pH as well. When the ambient pH is $\geq$7, urease induced hydrolysis of urea drives the local pH even higher (53). While the organism has developed effective mechanisms to survive at low pH, its mechanisms to survive at high pH are not as effective (52).

Adherence

The ability of *H. pylori* to bind specifically to gastric type epithelium is termed tissue tropism, a property which prevents the organism from being shed during cell and mucus turnover or by gastric motility (54). Adherence may also be important in targeting toxins and leukocyte recruitment factors in host epithelium (54,55). An N-acetylneuraminyl-lactose-binding fibrillar hemagglutinin has been described for *H. pylori* as has a specific gastric glycerolipid receptor on gastric mucosal cells (56,57). Tight attachment of the fibrillar adhesin on the bacterium to the carbohydrate receptor on the mucosal cell results in the formation of an attaching-effacing lesion (adherence pedestal) which in turn leads to actin polymerization and epithelial cell disruption (58-60). Failure of adherence, while having no effect on the inflammatory response, results in less epithelial cell injury (61). Differences in the availability of specific receptors has been suggested as one means to explain genetic differences in susceptibility to infection with *H. pylori* (62).

NH_4^+/H^+ ATPase

H. pylori survives with difficulty at either low pH (48) or very high pH (53). It has recently been shown that the organism possesses a P type ATPase which may catalyze an NH_4^+/H^+ exchange. This activity would prevent excessive alkalinization of the organism from ammonia generated by urease-catalyzed hydrolysis of urea (63). Elucidation of the role of this enzyme as a potential virulence factor and as a target for therapy is eagerly awaited.

FACTORS INDUCING TISSUE INJURY

Lipopolysaccharide(LPS)

LPS is a family of glycolipids found in the cell envelope of Gram-negative bacteria, including *H. pylori* (64). LPS, primarily through the Lipid A component, stimulates the release of cytokines and possesses endotoxic properties. Other actions of LPS include interference with the gastric epithelial cell-laminin interaction, which may lead to loss of mucosal integrity; inhibition of mucin synthesis; and stimulation of pepsinogen secretion (64). Despite its toxigenic properties, the lipid A of *H. pylori* is substantially less potent than the lipid A of *E. coli*, which may account for the organism's adaptation for long-term residence in the stomach.

Other Leukocyte Recruitment And Activating Factors

H. pylori elaborates a number of LPS-independent soluble surface proteins with chemotactic properties to recruit monocytes and neutrophils to the lamina propria and to activate these inflammatory cells (65-68). These include *H. pylori* neutrophil activating protein (68), expressed by the *nap A* gene, and the immunologically active porins (67).

CagA and VacA Proteins

Approximately 50% of *H. pylori* strains produce a substance which induces vacuole formation in eukaryotic cells (69).Two proteins associated with this vacuolating cytotoxin have since been characterized, the first being CagA (70). This 120-140 kDa, highly antigenic protein is encoded by the *cagA* gene, which is present in about 60% of *H. pylori* strains in developed countries (70). An association between CagA and duodenal ulcer disease, atrophic gastritis, and adenocarcinoma has been suggested (70), although not all studies concur. Strains with *cagA* have also been reported to be associated with a higher density of bacterial cells (71), more intense inflammation, and greater interleukin-8 (IL-8) production (72). Discrepant results from other investigators and countries (73) raised the possibility that CagA may be only a marker for some other product. Indeed, mutant *H. pylori* strains without *cagA* still have the ability to cause cell vacuolation and to induce IL-8 production (74). Two genes which are closely linked to *cagA* - *picA* and *picB* - are now thought to be possibly responsible for the pro-inflammatory activity associated with *cagA* positive strains (70). *picA* or *picB* knockout strains possess greatly decreased ability to induce AGS cells to induce IL-8. These genes are but three of about 20 genes located on a 40kb region constituting a "pathogenicity island".

The protein responsible for vacuolation (VacA) has been purified and the gene encoding the toxin (*vacA*) has been cloned (70). This gene encodes a 140,000 molecular weight protein which is processed to a mature toxin of 90 kDa. All strains of *H. pylori* possess the *vacA* gene, but only about 50% express the mature toxin. Studies in mice have demonstrated that supernatants from strains expressing the toxin, but not those without, cause severe mucosal injury (75). No clinical correlations with this observation have yet been described.

The *vacA* gene has been further characterized (76). The gene has two families of alleles of the middle region (m1,m2) and three families of alleles of the signal sequence (s1a,s1b,s2). All s2m2 strains (there are no s2m1 strains) were non-toxin producers and devoid of *cagA* (70). Over 80% of s1m1 strains were toxin producers, while about 30% of s1m2 strains produced toxin. Initial studies suggested that patients with peptic ulcer were more likely to have *H. pylori* of the s1 type than the s2 type. Confirmatory studies of the possible association of an association of the s1m2 type with duodenal ulcer disease are lacking.

The most recently described virulence gene is *iceA* (*i*nduced by *c*ontact with epithelium), which has two distinct alleles (77). Very preliminary data suggest that *iceA* strains are very closely linked with duodenal ulcer disease and are independent of *cagA*. Much work remains in this exciting area of pathogenesis.

Heat Shock Proteins

H. pylori expresses two heat shock proteins (HspA and HspB) (78). They are highly antigenic, but their role in the pathogenesis of infection remains unknown. HspA binds nickel ions and is a chaperonin.

CHRONIC INFECTION

Twenty-two of the volunteers described above with acute *H. pylori* gastritis and hypochlorhydria have had follow-up biopsies a mean of 12 years after their acute infection (38). Approximately 80% of these subjects had evidence of chronic infection with chronic superficial gastritis, compared to 36% of a control group matched for age, sex, race, and profession. Thus, although some individuals spontaneously clear the organism, it appears that infection in most adults is long-lived.

HISTOLOGY

Antral biopsies of individuals chronically infected with *H. pylori* show focal epithelial cell damage as well as an inflammatory infiltrate in the lamina propria (79). This infiltrate (the severity of which, in general, correlates with the intensity of *H. pylori* colonization), consists of polymorphonuclear leukocytes, eosinophils, and mononuclear cells. The latter include B and T lymphocytes [frequently in the form of lymphoid follicles (80)], monocytes, and plasma cells. The lymphocytic component of the inflammatory response is referred to as MALT (Mucosa Associated Lymphoid Tissue). While biopsies from individuals not infected with *H. pylori* have occasional PMNs and aggregates of lymphocytes, lymphoid follicles are never found (80). Biopsies from the gastric body also usually demonstrate inflammation, but typically the inflammation is less severe than in the antrum, a marked contrast to the intense body inflammation seen with the acute infection. Reasons for down-regulation of the inflammatory reaction are unknown, but may involve the immune response. In patients with duodenal ulcer the gastritis is often severe in the antrum but may be absent in the body (79,81). Cure of *H. pylori* infection results initially in a reduction of PMNs followed by gradual resolution of the chronic inflammatory cell infiltration (82).

INFLAMMATORY MEDIATORS

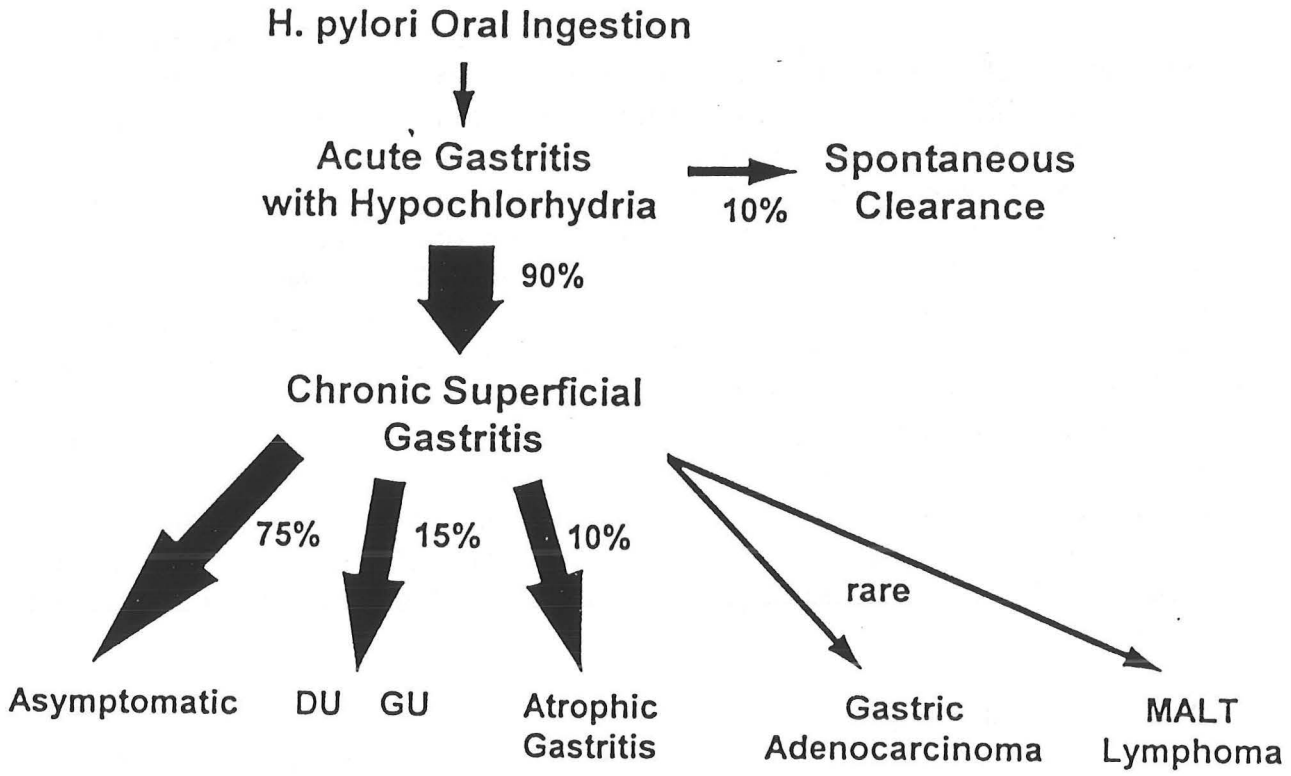
H. pylori stimulates the release of a variety of inflammatory mediators both directly by bacterial products [including *picA* and *B* gene products, lipopolysaccharide, neutrophil activating factor, and porins] and as a result of interaction with gastric epithelial

cells (55,83). In response, there is induction of IL-1, IL-8, and TNF_{alpha} which recruit and activate neutrophils. In addition there is the generation of reactive oxygen metabolites and the up-regulation of neutrophil expression of CD11b/CD18 (55). The latter enhances ICAM-1 dependent neutrophil adherence. With neutrophil adhesion comes changes in microvascular permeability and mast cell degranulation. This rich mixture of cytokines may also play a role in down-regulating somatostatin, thereby leading to enhanced gastrin release (see section on gastric secretion).

NATURAL HISTORY OF CHRONIC INFECTION

Most individuals with chronic *H. pylori* infection remain asymptomatic throughout their life (Figure 5). About one in six develop peptic ulcer disease. Atrophic gastritis, gastric adenocarcinoma, or gastric lymphoma are less frequent outcomes of infection.

Figure 5. Proposed natural history of H. pylori infection in humans.



PEPTIC ULCER DISEASE

In the majority of studies, virtually all patients with peptic ulcer disease who are not taking NSAIDs are infected with *H. pylori*. In addition, cohort studies have shown that infection precedes the development of an ulcer (84,85). Finally, the recurrence rate of ulceration is dramatically decreased following successful cure of infection. Thus, there is little debate now that *H. pylori* is an important risk factor for peptic ulcer and when present should be treated.

What remains unclear is why some patients with *H. pylori* infection will develop ulcers but most will not. An increasingly important possibility concerns strain variation. A number of studies now suggest that certain strains (?*cagA*, ?*iceA*) are more likely to be associated with duodenal ulcers (see above). Environmental factors such as smoking may also play a role. Finally, variations in host response to infection may be important. About a third of patients with duodenal ulcer are acid hypersecretors and perhaps most are duodenal bicarbonate hyposecretors (86). The interaction among strains and host response represents an area of fruitful research.

CHRONIC ATROPHIC GASTRITIS

In some individuals, chronic superficial *H. pylori* gastritis progresses over time to atrophic gastritis, with an annual increase in prevalence among otherwise normal subjects of 1-3% (87-90). Such progression leads to three patterns of atrophic gastritis: body predominant (Type A), antral predominant (Type B), both body and antrum (Type AB). In one study, the relative proportions of these patterns was 31%, 45%, and 24% (91). The pattern of development of chronic atrophic gastritis correlates well with the pattern of superficial gastritis (e.g., antral predominant superficial gastritis progresses to antral predominant atrophic gastritis). As the degree of atrophy progresses in type A or AB atrophic gastritis, the presence of *H. pylori* decreases. This may be due to hypochlorhydria creating an uninviting milieu for the organism (52,53). While the ability to detect *H. pylori* histologically is low in these patients, the prevalence of antibodies remains very high, suggesting current or prior *H. pylori* infection (91). The mechanism by which gastric atrophy occurs is unclear and is probably multi-factorial. The major factor may be environmental as the proportion of the infected population with atrophic gastritis varies remarkably in different geographic areas (e.g., Peru vs. the United States). There may also be differences in characteristics of the strains of *H. pylori* circulating in the region. One recent study found *H. pylori* antibodies which cross-reacted with gastric autoantigens (92).

Type A (body predominant) atrophic gastritis may be associated with pernicious anemia (PA). Such patients have antibodies directed against the proton pump, pepsinogen, and intrinsic factor (93). In these patients, loss of secretory function begins with acid, followed by pepsinogen, and, finally, intrinsic factor (94). PA is, thus, a marker for the most severe, end-stage form of Type A atrophic gastritis. There has been a long-

held belief that the pathogenesis of chronic atrophic gastritis associated with PA is "autoimmune", since there are antibodies to the secretory elements. Furthermore, the prevalence of *H. pylori* is low by both tissue staining and serum antibodies, suggesting not even a remote infection with the organism (95). While the concept is now being challenged, the marked regional variation in the prevalence of PA suggests that the genetics of the host play a critical role. Pernicious anemia is also found in areas where *H. pylori* is uncommon (e.g., the region surrounding the Mayo Clinic). Nevertheless, antibodies to secretory elements appear to develop after the atrophic process begins, leading one investigator to suggest that the "intracellular structures of the gastric mucosa may, as a result of cell damage, be exposed to immunocompetent cells, which do not recognize these structure as 'self'" (96). Second, a recent study of first-degree family members of PA patients found the expected high prevalence of body atrophic gastritis and parietal cell antibodies, but an unexpectedly high prevalence of serum antibodies to *H. pylori* (97). It is plausible, therefore, that PA may be the end result of a number of initiating events. One of these events may be that in one subset of patients *H. pylori* gastritis progresses to a severe form of atrophic gastritis associated with "autoimmunity" and the development of PA. One would expect that *H. pylori*-related pernicious anemia would be associated with antral evidence of present or past infection whereas "pure" autoimmune pernicious anemia would have a normal antral mucosa. It is likely that pernicious anemia, like peptic ulcer, will be the end result of several pathways. Studies of the epidemiology of pernicious anemia and *H. pylori* infection will be required to elucidate these pathways. The presence or the absence of antibodies to *H. pylori* in pernicious anemia patients alone cannot address the etiology.

GASTRIC ADENOCARCINOMA

It has long been known that gastric adenocarcinoma and gastritis were closely related. It has been postulated that the sequence of mucosal histologic events leading to the intestinal type of gastric adenocarcinoma is: chronic superficial gastritis -atrophic gastritis - intestinal metaplasia - dysplasia - adenocarcinoma. The proof that *H. pylori* was the most common cause of chronic superficial gastritis allowed the previous epidemiologic associations to be transferred from gastritis to *H. pylori*. *H. pylori* is now accepted as the cause of chronic superficial gastritis which is some patients progresses to atrophic gastritis (see above). There is an epidemiologic association between *H. pylori* and adenocarcinoma of the gastric body and antrum, but not the cardia (98-100).

Table 2. Seroprevalence of *H. pylori* 6-14 years before diagnosis in patients with gastric cancer and matched controls [nested case control studies from references (98-100)].

	Parsonnet	Nomura	Forman
Cohort Size (N)	128,992	5,908	22,000
Follow-Up (Y)	14.2	13	6
Cancer (N)	246	137	29
Selected as Cases	109	109	29
% H.p.+:Cases	84%	94%	69%
% H.p.+:Controls	61%	76%	47%
Odds Ratio:			
All AdenoCa	3.6	6.0	2.8
Intestinal Type	3.1	4.5	-
Diffuse Type	8.0	-	-

Because most of the patients with gastric cancer and their matched controls were from older age groups, the absolute differences in *H. pylori* prevalence were not striking (Table 2). Now that the general prevalence of *H. pylori* is decreasing, the difference in *H. pylori* prevalence between patients with and without gastric cancer may widen. Support for this concept is found in a recent study from Japan of young patients with gastric cancer in whom the prevalence of *H. pylori* was 88.4% compared to only 26.9% in young, age-matched controls (101).

As important as *H. pylori* infection appears to be, other factors must also play a role. The proportion of patients who progress to gastritis with atrophy varies markedly in different geographic areas despite similar prevalence of *H. pylori* infection. In areas where cancer is rare, only a small proportion of patients progress to atrophic gastritis, much less to intestinal metaplasia, dysplasia, and cancer. As with peptic ulcer, *H. pylori* gastritis is in most individuals a necessary, but far from sufficient, factor in the pathogenesis of gastric adenocarcinoma. It is unknown whether the marked differences in outcome of the infection relate to differences in the predominant strain circulating in a region or to other environmental factors (e.g., salt intake).

The diffuse type of gastric cancer is also associated with *H. pylori* (Table 39-2), but not with atrophic gastritis. Sipponen biopsied non-cancerous tissue in the antrum of patients with the diffuse type of gastric cancer and found chronic superficial gastritis in 52% and atrophic gastritis in only 27% (102). In contrast, in patients with the intestinal type, only 26% had superficial gastritis and 61% had atrophic gastritis.

GASTRIC LYMPHOMA

It is now well-recognized that primary gastric B-cell lymphoma arises in gastric MALT (mucosa associated lymphoid tissue) which occurs only in stomachs infected with *H. pylori*. Two groups now have 12-24 month follow-up data suggesting that complete regression of low-grade gastric lymphoma occurs in 60-70% of patients following successful cure of *H. pylori* infection (103-105). A trial of eradication therapy is now considered standard of practice in patients with primary low-grade gastric lymphoma who are infected with *H. pylori*.

OTHER ASSOCIATED CONDITIONS

Several studies have found the *H. pylori*-infected individuals were shorter in stature than those without infection (14,106). While this could merely represent another manifestation of low socioeconomic status as a child, one study found the influence *of H. pylori* to be independent of socioeconomic factors (14). The mechanisms for this association, if valid, are unknown. Another putative association with *H. pylori* infection is coronary artery disease (107,108). While much more data are needed to be convincing, one group reports the association even after correcting for the confounding factors of age and other cardiovascular risk factors (108). This group of investigators suggests that the link may be via hyperfibrinogenemia induced by the chronic inflammation of *H. pylori* gastritis (108,109). Careful studies controlling for all possible variables are needed to confirm these findings.

GASTRIC SECRETION

GASTRIN

Fasting serum gastrin levels are higher by about 35-45% in normal subjects infected with *H. pylori* than in uninfected controls (110-112). When intragastric pH was maintained by in-vivo titration at pH 5.0 or 7.0, there were substantially higher post-prandial gastrin responses to the meals in *H. pylori* infected subjects than in negative controls (110,111). When the intragastric titration pH was lowered to 2.5, as would occur in the natural state as acid is secreted in response to a meal, there was almost complete (95%) suppression of meal-stimulated gastrin release in uninfected subjects (111). By contrast, infected subjects exhibited only a 52% suppression of gastrin release at pH 2.5.

Infusion of gastrin releasing peptide (GRP), the mammalian analog of bombesin, stimulates many of the stimulatory (and inhibitory) mechanisms elicited by meals and has been used by some investigators as a surrogate for meal studies (113). As gastrin is released and acid is secreted, gastric pH falls. It therefore accomplishes in a less cumbersome manner what is achieved by changing the intragastric titration pH of a meal from 7.0 to 2.5 (111). In one study, the median plasma gastrin concentration after GRP infusion in *H. pylori*-infected normal subjects was more than three times that which occurred in non-infected controls (112). Eradication of *H. pylori* restored fasting and GRP-stimulated serum gastrin to levels found in non-infected subjects (112). The authors conclude that *H. pylori* infection in some way interferes with the normal inhibition of gastrin release at low pH, perhaps via reduced somatostatin release (See Chapter 38).

ACID SECRETION

When meal-stimulated acid secretion is measured by in-vivo titration at a high pH (5.0-7.0), no differences are seen between infected and non-infected normal subjects (110,111). However, when carried out at a pH of 2.5, infected subjects have a significantly higher acid response to the meal than non-infected controls (111). This reflects a failure of normal inhibition of acid output at low pH in *H. pylori*-infected subjects, a situation analagous to that with serum gastrin (see above). Similar results have been noted using GRP (112); the median acid output to 40 pmol/kg/h GRP was three times greater in *H. pylori*-infected normal subjects. This phenomenon may be a result of greater gastrin release or, since gastric pH falls in response to GRP-stimulated acid output, may reflect impairment by *H. pylori* of "normal" inhibition of acid output at low pH. Differences between the groups remain when GRP is given in doses high enough to elicit maximum acid output (112). Recent studies with GRP and a previous one with bombesin have shown that with there is an upward shift in the response to these stimuli. *H. pylori* infected individuals produce approximately 90% of their maximum acid output compared to about 30% in those without *H. pylori* infection. Following cure of the infection, both duodenal ulcer patients and those with *H. pylori* infection but without ulcer disease return to the normal pattern of GRP-stimulated acid secretion (about 30% of MAO) (112).

While abnormalities have been noted in meal or GRP-stimulated acid secretion, basal acid output (BAO) in *H. pylori*-infected normal subjects has been reported to be not significantly different from uninfected subjects in one series (114), significantly higher in another (112) and somewhat lower in two other series (110,111). Submaximal, peak (PAO) and maximal (MAO) acid output to fixed doses of exogenous gastrin or pentagastrin are also not significantly different in normal subjects infected with *H. pylori* compared to uninfected controls (110-112,114). One variable which must be considered in interpreting studies of acid secretion in normal subjects infected with *H. pylori* is the degree of inflammation. A recent study has confirmed earlier reports from Scandinavia that BAO, PAO, and also pepsin secretion are inversely correlated with the severity of inflammation (115). Data on acid secretion after eradication of *H. pylori* in normal subjects are sparse. One group studied 30 *H. pylori*-infected normal subjects before, one month, and three months after a course of triple therapy (116). No significant differences were noted in BAO or PAO after therapy in either the 18 subjects in whom *H. pylori* was eradicated or the 12 subjects in whom therapy was unsuccessful.

H. pylori infected patients with duodenal ulcer (DU) have fasting and GRP-stimulated gastrin levels similar to normal subjects infected with the organism (112). Acid secretory values, on the other hand, are different. Compared to *H. pylori* infected normal subjects, *H. pylori* infected DU patients have significantly higher basal, peak and GRP-stimulated acid secretion (112). When measured one year after successful eradication therapy, basal and GRP-stimulated acid secretion had normalized. Whether PAO in DU patients falls after cure of *H. pylori* infection remains an area of controversy, but it appears that in most there is either no change or a minor fall. Work in this area is ongoing.

SERUM PEPSINOGEN

With acute superficial gastritis, serum levels of both PGI and PGII rise. Since PGII is made by mucous cells throughout the stomach, not just in the oxyntic glands, serum PGII rises proportionately more than PGI. Thus, the serum PGI/PGII ratio falls. As atrophy occurs and progresses, the levels of PGI fall substantially, while PGII levels fall only modestly. Thus, the serum PGI/PGII ratio continues to fall with increasing degrees of atrophy.

PHENOTYPIC EXPRESSION OF GASTRITIS AND ACID SECRETION

There is an inverse correlation between the severity of *H. pylori* gastritis in the body and the level of acid secretion. Thus, patients with duodenal ulcer have the mildest degree of gastritis and the highest acid output while patients with atrophic gastritis have the lowest acid output. Asymptomatic patients with chronic superficial gastritis have intermediate levels of acid secretion, but there is still an inverse correlation with severity of gastritis (115). There are two possible explanations for this association. First, the degree of inflammation may dictate the level of acid secretion. This is certainly the case in end-stage atrophic gastritis where atrophy of parietal cells has occurred. The second possibility is that the level of acid secretion determines the severity of gastritis. There is some support for this hypothesis. Patients with duodenal ulcer have robust acid secretion and virtually never develop body atrophic gastritis (117-120). On the other hand, patients with gastric ulcer (118,121), patients after vagotomy (122,123), or patients on long-term acid suppression therapy (124-126) exhibit more frequent progression. A unifying hypothesis for this phenomenon is based on the observation that *H. pylori* grows poorly at low pH (48,127). Thus, individuals with higher levels of acid secretion will have a relative paucity of organisms in the proximal stomach and, concomitantly, a milder inflammatory response and less propensity to development of atrophy. In individuals with lower levels of acid secretion (e.g., long-term antisecretory therapy), *H. pylori* will flourish proximally (128,129) leading to a more intense inflammatory response and greater propensity to progress to atrophy. As this occurs, there may also occur relative healing of the antral mucosa as organisms migrate proximally. If this hypothesis is correct, and because atrophic gastritis is a precursor for gastric adenocarcinoma, it has been sugggested that patients who will be on long term acid suppressive therapy be tested for the presence of *H. pylori* and, if present, be treated (129,130). This area continues to be one of active investigation.

DIAGNOSIS

AVAILABLE TESTS

Diagnostic tests for *H. pylori* may be divided into those which do or do not require samples of gastric mucosa. While tissue is generally obtained from patients undergoing endoscopic biopsy under conscious sedation, modestly less invasive methods are available for conscious patients such as the use of a small bowel biopsy tube or a biopsy forceps passed through a modified nasogastric tube positioned either in the gastric body or antrum (131). Generally, biopsy is unnecessary unless one needs to isolate the organism for susceptibility testing. Culture is generally the least sensitive of the techniques utilizing mucosal biopsy, primarily because an experienced laboratory is required to routinely isolate this fastidious organism. Culture is required when antimicrobial

susceptibility information is desired.

Mucosal biopsy and histological examination of the specimen for the presence of *H. pylori* and/or gastritis has been the diagnostic method of choice until recently. Recommendations to maximize diagnostic yield include the use of large-cup biopsy forceps, obtaining at least three tissue samples (from the lesser curve angularis, the greater curve pre-pyloric antrum, and the greater curve body), proper mounting and preparation of the samples, and use of an appropriate stain (132). The standard hematoxylin and eosin (H&E) stain is excellent to determine histologic chronic or chronic active inflammation (gastritis) and will demonstrate *H. pylori* if enough organisms are present. A silver stain (e.g., Warthin-Starry) is better at detecting the organism if small numbers of bacteria are present, but does not show tissue histology to advantage. Attributes of both stains are found in the Genta stain, which combines the H&E stain with a silver (Steiner) stain and Alcian blue (133). This stain not only shows mucosal morphology, but is equivalent to the Warthin-Starry stain in detecting *H. pylori*, especially when there is a low density of bacteria, a small biopsy specimen, abundant debris or mucus on the gastric surface and pits, or extensive intestinal metaplasia.

Mucosal biopsies may also be tested for the presence of urease by a rapid urease test such as the agar gel slide tests (e.g., CLOtest, *hp*fast) or the membrane test, PyloriTek. Rapid urease tests consist of a urea-rich medium with a pH sensitive dye. If urease is present in the mucosal biopsy, it catalyzes the hydrolysis of urea into ammonia and carbon dioxide (134). The resultant increase in pH of the medium from ammonia generation changes the color of the indicator. Recommendations to maximize the sensitivity of rapid urease tests are to warm the slide and to use two regular or one jumbo biopsy specimen. The PyloriTek test is more sensitive than the gel-based tests at 1-2 hours (when it should be read), but has no greater overall sensitivity when the others are read at 24 hours. A low bacterial count or recent use of antibiotics or proton pump inhibitors may render urease tests falsely negative. The relative accuracies of acute or chronic inflammation on histology, a silver stain, and a rapid urease slide test as determined in one center are shown in Table 3 (135). As can be seen, the Warthin-Starry silver stain has the best combination of sensitivity and specifity. Rapid urease tests have specificity and sensitivity of greater than 90%, but false negatives and positives do occur. Rapid urease testing is the least expensive, is an excellent screening test, and is the diagnostic test of first choice when an endoscopy is performed. Mucosal biopsies can be retained, and if the rapid urease test is negative, sent for histological assessment.

Tests which do not require a mucosal biopsy include serological tests and urea breath tests. Chronic *H. pylori* infection elicits a circulating IgG antibody response that can be quantitatively measured by ELISA tests (136-138). Tests for serum IgA or IgM antibodies are unreliable so only serum IgG antibodies should be determined. Serological tests are as sensitive and specific as biopsy-based methods (Table 39-3) and have been adapted for rapid use in the office. One study found the FlexSure HP to be about 90% specific and accurate, significantly more so than the Quick Vue test (139). In-the-office tests have recently been modified to use whole blood instead of serum (140), but their sensitivity may be lower than comparable serum-based tests. While it is possible to detect antibodies to *H. pylori* in saliva, gingival transudate, or urine, no reliable tests are yet commercially available.

Serologic tests are very useful for the initial diagnosis of *H. pylori* infection, but are less useful to confirm cure after antimicrobial therapy. While it has been reported that a fall in paired titers of 20% or more six months after completion of therapy may be sensitive in confirming cure of the infection (141), it is not a practical method. It requires quantitative measurement of titer, using paired specimens (i.e., "before" serum specimens must be frozen and stored to be run at the same time as "after" specimens) and must be delayed at least six months. Qualitative tests are unsuitable since probably no more than a third of patients successfully cured of their infection actually convert to a "negative" test (141).

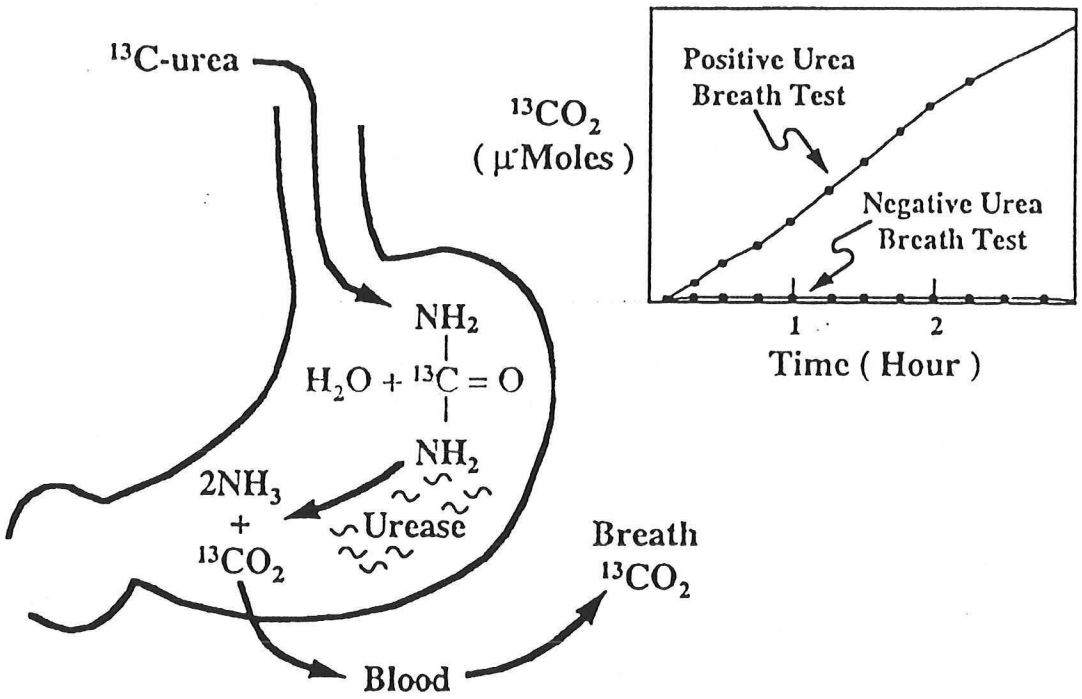
Table 3. Accuracy of diagnostic tests for *H. pylori*. From Reference (135).

Parameter	Sens.	Spec.	PPV	NPV
Chronic Inflammation	100%	66%	84%	100%
Acute Inflammation	87%	94%	96%	80%
Silver Stain	93%	99%	99%	89%
Rapid Urease Test	90%	100%	100%	84%
Serum IgG Antibody	91%	97%	95%	85%
Urea Breath Test	90%	96%	98%	84%

Sens. = Sensitivity; Spec. = Specificity; PPV = Positive Predictive Value; NPV = Negative Predictive Value

The other non-invasive means of detecting *H. pylori* are the urea breath tests (UBT), which should be commercially available soon. With these tests, urea labeled with either ^{13}C or ^{14}C is ingested (142). If urease is present in the stomach as a consequence of *H. pylori* infection, labeled carbon dioxide will be split off and absorbed into the circulation where its presence can be determined by analysis of expired breath (Figure 6). This test is quite accurate, although small numbers of organisms may not produce enough urease to be detected by the UBT (i.e., a false negative result). ^{13}C labeled urea has the advantage of not being radioactive but requires a mass spectrometer for analysis; ^{14}C can be measured with a scintillation counter but does subject an individual to a small, long-lasting dose of radioactivity. These tests should become the preferred means of evaluating the success of antimicrobial therapy in clinical practice.

Figure 6. The urea breath test. From reference (143).



Finally, some endoscopists erroneously believe that a diagnosis of *H. pylori* gastritis can be made by the gross appearance of the gastric mucosa at endoscopy. Results of the one study which has examined this hypothesis critically suggest that antral nodularity has a positive predictive value of 90%, but a sensitivity of only 32% (144). The best endoscopic predictor is the presence of an ulcer.

DIAGNOSTIC STRATEGY

The selection of the appropriate test in a given patient depends upon the clinical situation. For patients in whom an endoscopy is clinically indicated to diagnose or treat a peptic ulcer, it is reasonable at the same time to obtain mucosal biopsies for a rapid urease test and histology. A rapid urease test is the least expensive of the biopsy tests and should be performed first; extra biopsies should be taken and held for submission for histologic examination if the rapid urease test is negative. Culturing for antibiotic susceptibility testing is not currently practical but may become necessary if resistance to metronidazole or clarithromycin increases.

For patients in whom it is not indicated for other clinical reasons, endoscopy should not be performed solely to diagnose infection with *H. pylori*. Serologic tests are quick, inexpensive, and reliable; they are the initial screening test of choice. If concern remains that a positive serologic test may be only a "scar" from prior infection and does not accurately reflect the current status, a urea breath test can document the presence of active infection.

TREATMENT

Cure of *H. pylori* infection is not easy and requires combinations of one or two antibiotics with one or two non-antibiotic adjunctive agents; single agents are ineffective. Several observations have emerged from the multiple treatment trials:(a) Results from different studies of what outwardly appears to be the same drug combination often vary enormously. Only regimens which give consistently good results from country to country and from study to study should be used; (b) Successful cure of infection requires at least two agents, and if one week therapy is desired, three or four agents are needed;(c) All successful regimens include clarithromycin and/or metronidazole;(d) While once a cure rate of 80% was considered acceptable, rates of 90% or higher are now achievable, especially if the organism is susceptible to the antibiotics used;(e) Resistance to metronidazole or clarithromycin may lead to reduced efficacy with that antibiotic; (f) Compliance is important for sucessful cure of the infection. Thus, regimens should be designed so that side effects which may reduce compliance are minimized.

DEFINITION OF CURE

It has become clear that failure to detect *H. pylori* immediately after a course of antimicrobial therapy does not mean that the infection has been cured. In many instances the organism has only been suppressed, with follow-up studies performed several weeks later readily disclosing its presence. *H. pylori* may find "sanctuary sites" which preclude cure, but from which it ultimately emerges to regain its foothold. Thus, cure of infection is defined currently as absence of the organism by tests performed no sooner than 4 weeks after cessation of antimicrobial therapy. Because PPIs alone can suppress the infection, PPI therapy should be discontinued for at least one week before evaluation of effectiveness of therapy.

ANTIBIOTICS USED IN REGIMENS TO ERADICATE *H. pylori*

Amoxicillin: *H. pylori* is very sensitive *in vitro* to this antibiotic, but *in vivo* it has little effect when used as monotherapy. This may be due to relative inactivity of the antibiotic at low pH; better results are achieved if antisecretory agents are given with amoxicillin-containing regimens. Resistance to amoxicillin has been observed, but is rare. The most common side effects are skin rash, candidiasis, and diarrhea.

Tetracycline: Tetracycline is effective *in vitro* against *H. pylori*, is active at low pH, and resistance has not yet been reported. It is quite useful as part of triple therapy with bismuth and metronidazole but is contraindicated in children because of the staining of teeth.

Metronidazole: *H. pylori* ordinarily is highly sensitive to metronidazole, which is actively secreted into gastric juice and saliva and whose activity is independent of pH. Use of metronidazole as a sole agent selects out mutant organisms which are resistant to metronidazole. Resistance develops less often when metronidazole is given with bismuth or a second antimicrobial agent. Primary resistance of *H. pylori* to metronidazole is generally associated with a reduction in cure rates (145). This is important, as the

frequency of primary resistance to metronidazole is increasing substantially throughout the world. For example, one study from the United States found primary resistance to metronidazole in 54% of isolates (146). On the other hand, metronidazole resistance appears to be less of a problem when metronidazole is combined with clarithromycin and one other active agent. Side effects of metronidazole include a metallic taste, diarrhea, and nausea, the latter occurring primarily at doses over 1 gram/day. Some individuals may experience an Antabuse-like effect with ingestion of alcoholic beverages. Tinidazole, a nitroimidiazole not available in the United States, gives results which are comparable to metronidazole.

Clarithromycin: This antibiotic is a macrolide with an antibacterial spectrum similar to erythromycin but which is more acid stable, better absorbed, and more active against *H. pylori*. When given in a high dose (2 gm/day) as monotherapy, clarithromycin cures *H. pylori* infection in 54% of subjects. As with metronidazole, *H. pylori* can become resistant to clarithromycin when the latter is given as a single agent, although primary resistance to clarithromycin is found less frequently than with metronidazole. Side effects include taste perversion in a majority of patients.

ADJUNCTIVE AGENTS USED IN REGIMENS TO ERADICATE *H. PYLORI*

Bismuth: Bismuth compounds are topical antimicrobial agents that act directly upon bacterial cell walls to disrupt their integrity by accumulating in the periplasmic spaces and along membranes. Bismuth is most widely available in the United States only as bismuth subsalicylate (PeptoBismol^{R}), whereas elsewhere colloidal bismuth subcitrate is widely used. Antibacterial concentrations of bismuth are achieved in antral mucus only for about 2 h after dosing. Side effects with these two bismuth compounds are minimal, although blackening of the stool may occur.

H,K ATPase (Proton Pump) Inhibitors (PPIs): Omeprazole, the first of the substituted benzimidazoles, may be used as a model for all PPIs (See Chapter 38). *In vitro*, omeprazole inhibits the growth of *H. pylori* and, to a lesser extent other bacteria, at pH below 7 (48); omeprazole will inhibit growth of *H. pylori* at pH 7 only in its active sulfenamide form (48). Omeprazole's mechanism of action on *H. pylori* is not through inhibition of urease, since the inhibitory effect is seen with a urease-deficient strain of *H.pylori* or in the absence of urea in the medium.

Based on the above *in vitro* data, it could be predicted that omeprazole would have little effect *in vivo* on *H. pylori*. The drug is enteric coated to prevent dissolution until reaching the alkaline small bowel, where it is then absorbed. Thus, when gastric pH is low, no omeprazole would be expected in the stomach. If gastric pH were high enough to permit dissolution of the enteric coating in the stomach, it would not be in its active (sulfenamide) form. Theoretically, the only way in which omeprazole could exert a direct intragastric effect on *H. pylori* is if the sulfenamide were secreted from the parietal cell into the gastric lumen, a phenomenon which has not been described. Nevertheless, when omeprazole (or other PPIs) are employed as single agent *in vivo*, the *H. pylori* is suppressed (147). PPIs have proven to be especially useful as part of combination

therapy with antimicrobial agents to cure *H. pylori* infection. One major activity is related to increasing intragastric pH which may enhance the effectiveness of the local immune response, reduce the washout of antibiotics from the mucosa, and improve the minimal inhibitory concentrations of pH sensitive antibacterial agents. The decreased gastric juice volume that results from these antisecretory drugs may also increase intragastric concentrations of antibacterial agents.

Histamine-2 Receptor Antagonists (H2RAs):This class of drugs has long been used to promote healing of peptic ulcers. They have no effect by themselves against *H. pylori*, but have been used in some studies instead of PPIs in combination with antibiotics.

Ranitidine Bismuth Citrate (RBC): This is a novel compound with characteristics of both ranitidine (anti-secretory) and bismuth. While RBC is quite effective *in vitro* against *H. pylori*, studies in humans have shown no effect in curing *H. pylori* infection. RBC is useful when combined with antibiotics, such as clarithromycin. Side effects are minimal.

THERAPEUTIC REGIMENS TO ERADICATE *H. pylori*

Regimens to eradicate *H. pylori* may be classified by the number of antibiotics and adjunctive agents employed.

One Antibiotic + One Adjunctive Agent (Dual Therapy): This combination consists of an antibiotic plus a PPI or RBC. The regimen initially touted was amoxicillin plus omeprazole. Initial studies suggested that infection was cured in over 80% of patients (148) and one study using a very high dose of omeprazole reported over 95% cure (149). However, such good results have not been confirmed (150-153) and this regimen can no longer be recommended. More consistent results have been achieved with clarithromycin (500 mg tid) plus omeprazole (40 mg once daily), with cure rates after 14 days of therapy of about 75% in well-designed, well-controlled studies (154). This regimen is one of the first two approved by the U.S. Food and Drug Administration (FDA) for the treatment of *H. pylori* infection. Eradication rates of about 80% in equally well-conducted studies have been noted with 14 days of therapy with the combination of clarithromycin (500 mg tid) and RBC (400 mg bid) (155), the other regimen initially approved by the FDA. While these regimens will undoubtedly be heavily marketed, they do not achieve the goal of a 90% cure rate.

Two Antibiotics + One Adjunctive Agent (Triple Therapy): Therapy with metronidazole (250 mg tid), tetracycline (500 mg qid), and bismuth (2 tablets qid) ("traditional" bismuth triple therapy) produces cure rates of 85-90%, especially with organisms sensitive to metronidazole (145,156). Amoxicillin should be substituted for tetracycline in children to avoid staining of teeth. Depending on the dose of metronidazole, over 30% of patients taking this regimen will report some side effect (i.e., nausea, sore mouth, taste disturbance, diarrhea, and *Candida* infection), resulting in cessation of treatment in about 5% of patients (145). These side effects, the complexity of traditional triple therapy, and the increasing prevalence of *H. pylori* strains resistant to metronidazole make this otherwise excellent regimen less desirable.

A 10-day course of metronidazole, amoxicillin, and ranitidine resulted in cure of *H. pylori* infection in 89% of patients (157). Clarithromycin may be substituted for amoxicillin with comparable results. More recent studies have combined two antibiotics with a PPI (PPI Triple Therapy) instead of an H2RA, with generally good results so far. One early study found that a combination of clarithromycin 250 mg and tinidazole 500 mg twice daily plus omeprazole 20 mg once daily for one week cured *H. pylori* infection in 95% of patients (158). A recent large European trial compared five different regimens containing two antibiotics plus omeprazole given for 7 days (159) (Table 4). Best results were achieved with combinations containing clarithromycin plus either amoxicillin or metronidazole. Unfortunately, tetracycline was not included in any of the regimens studied. It is likely that two antibiotics plus RBC will be more effective than clarithromycin alone plus RBC, but such studies are yet lacking.

Table 4. The MACH 1 study. From Reference (159).

Regimen	N	Eradication	95% CI
OAC 500	110	96%	93-100
OMC 250	111	95%	90-99
OMC 500	118	90%	84-95
OAC 250	111	84%	77-91
OAM	119	79%	72-86
OP	115	1%	0-3

O = Omeprazole 20 mg b.i.d.
A = Amoxicillin 1000 mg b.i.d
M = Metronidazole 400 mg b.i.d.
C = Clarithromycin 250 mg or 500 mg b.i.d.
P = Placebo

All regimens were given for 7 days.

Before such data are accepted as definitive, two areas of concern should be noted. First, these data are *per protocol*, not intention-to-treat and represent the best case scenario. Second, results achieved in U.S. patients invariably are less dramatic than those found in patients from other parts of the world.

Two Antibiotics + Two Adjunctive Agents (Quadruple Therapy): Several studies have added an antisecretory agent to traditional bismuth triple therapy. For example, in one United States study, this regimen plus ranitidine taken for 14 days cured *H. pylori* infection in 89% of 62 patients (160). Substitution of clarithromycin (500mg tid) for metronidazole gives similar results (161). Early studies of traditional bismuth triple therapy with omeprazole (PPI Quadruple Therapy) have shown cure rates of over 95% after only 7 days of therapy (162). It has also been suggested that results with such a regimen may be only minimally affected by metronidazole-resistant organisms. More data are needed.

THERAPEUTIC STRATEGY

It is naive at the extreme to declare any one regimen "best" to treat *H. pylori*. Regimens that are in fashion one day may be out of date or proven ineffective the next. This is a rapidly changing field and recommendations must be considered in that light. At the current time, the preferred regimens to cure *H. pylori* infection are combinations of two antibiotics and one or two adjunctive agents taken for 7-14 days. Although regimens comprised of two antibiotics with a PPI are expensive, they are easy to take and have few major side effects. Unless a patient has taken clarithromycin previously, one of the two regimens containing this antibiotic (OAC, OMC - Table 4) or traditional triple therapy plus a PPI is recommended. These regimens appear to be effective even if *H. pylori* is resistant to metronidazole. While data from Europe suggest that 7 days of therapy is adequate for triple therapy, studies from the United States, where cure rates are generally lower than in Europe, have not been reported. Thus, 14 days therapy is recommended in the United States with any regimen selected until such studies are performed. OAC has a lower cure rate than OMC unless given for 14 days.

FOLLOW-UP OF PATIENTS AFTER ANTIMICROBIAL THERAPY

The first decision to be made following therapy is whether or not any follow-up test is needed. It has been suggested that for many patients with uncomplicated ulcer disease, it is reasonable just to monitor for recurrent symptoms (See Chapter 40). Failed therapy in such patients will almost uniformly be associated with recurrence of the ulcer and ulcer symptoms. If the patient remains asymptomatic, one may assume that cure was achieved; if symptoms recur, a test to determine persistence or recurrence of infection can be performed. On the other hand, recurrent ulcer will be associated with additional visits to the doctor, additional tests and medications, time lost from work, as well as the potential for an ulcer complication. When simple, non-invasive methods such as the urea breath test are widely available there may be little reason not to confirm the results of therapy in patients with ulcer disease.

For patients with a history of bleeding or perforated ulcer associated with *H. pylori*, and if maintenance H_2 receptor antagonist therapy is to be stopped at some point, it is important to first document cure of the infection. If endoscopy is required, mucosal biopsies can be taken; otherwise, a urea breath test is indicated.

REINFECTION

Reinfection rates in developed countries are low. In one study, 173 patients whose infection was "cured" as defined above were followed for a mean of 5.1 years (163).

Recurrent infection was diagnosed in 9 (5.2%) after a mean of 8.7 months. It was possible to compare the initial and recurrent isolates in eight patients. In three, the recurrent isolate was different from the original isolate, but identical to that of the patient endoscoped immediately before (i.e., endoscopic transmission). In the other five, the inital and recurrent isolates were identical. Thus, there were no cases of community acquired reinfection with *H. pylori*. Reinfection rates in developing countries are substantially higher (145).

TREATMENT OF PATIENTS WHO FAIL AN INITIAL COURSE OF THERAPY

Two approaches are available in choosing second-line therapy. If antibiotic susceptibility results are available, the choice of a regimen will be determined by the antibiotics to which the organism is sensitive. If susceptibility results are unavailable, one may select a regimen containing whichever of metronidazole or clarithromycin was not used initially.

WHEN TO TREAT FOR H. PYLORI INFECTION

Definitely Indicated

Data are clear that the majority of patients with peptic ulcer disease should be treated with antimicrobial therapy, as recurrence rates are substantially reduced. The occasional patient with very mild, seldom recurrent disease can probably be left alone as can patients well-controlled on maintenance anti-secretory drugs who would tolerate anti-microbial therapy poorly or who have limited life expectancy. Patients with low-grade B cell lymphoma of the MALT type also should receive a trial of eradication therapy, as many (?most) will experience regression.

Indications Defensible

Data are emerging that patients on long-term anti-secretory therapy who are infected with *H. pylori* should receive antimicrobial therapy to lower the risk of development of atrophic gastritis. On the other hand, there is no evidence that such patients actually proceed on to development of gastric adenocarcinoma or have other sequelae of atrophic gastritis. There is also no proof that cure of *H. pylori* infection in relatives of patients with gastric adenocarcinoma will prevent the disease, although many physicians would believe there is little to lose by treatment. The relative rarity of this disease would limit the number of patients who need to be treated.

Indications Questionable

Treatment of patients with dyspepsia but no documented ulcer is the subject of intense debate at the present time, as is the overall approach to the patient with new onset dyspepsia (164-167). A detailed discussion of the issue is beyond the scope of this presentation as is the concept that all individuals, whether symptomatic or not, should be treated if found to be infected.

IMMUNIZATION

A long-term, worldwide solution to *H. pylori* related disease can be effected only by prevention of acquisition of the infection; antimicrobial therapy of existing infection is cumbersome, expensive, and ineffective in countries where re-infection rates are high. One possible solution is to develop a successful preventative vaccine. Animal models are being used to develop vaccines by defining appropriate antigens (e.g., urease, heat shock proteins, vacA) and to find effective and safe adjuvants (168). It is of interest that in mice, vaccination can be therapeutic, (i.e., cure an ongoing infection) (169). It appears that the infected stomach does not mount an effective secretory IgA response to the infection. Vaccination reverses this and an effective mucosal immune response to one of the surface proteins of *H. pylori* leads to both prevention of infection as well as cure of ongoing infection. Whether the encouraging results from animal experimentation will be applicable to man remains to be evaluated.

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