CHAPTER 29

Helicobacter pylori Infections

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INTRODUCTION

Since its isolation in 1982[1, 2] *Helicobacter pylori* has been detected in every human population studied, and associated with inflammation of the gastroduodenal mucosa. The organism had been seen by many investigators prior to 1982[3] but its potential importance in peptic ulcer disease had been overlooked, and peptic ulcer, perhaps the main gastric disease, was assumed to be caused by acid. In addition, the acid-secreting stomach was assumed to be sterile[4] since only transient oropharyngeal organisms had ever been cultured from gastric juice.

It is now well accepted that *H. pylori* colonizes the mucous layer of the human stomach and causes inflammation termed *active chronic gastritis.*[5] *H. pylori* can easily be identified using simple techniques available in all microbiology laboratories. The bacterium infects more than half of the population of the world, is more common in tropical, developing countries, and is believed to cause peptic ulceration and gastric cancer. In the tropics it may be associated with reduced gastric acid,[6] increased diarrhea, and malnutrition.[7] *H. pylori* can be diagnosed by direct examination of gastric mucosal biopsy tissue obtained at endoscopy, or noninvasively using serology or the urea breath test. Cure of the infection is possible in most patients with a 2-week treatment using combination therapies with antimicrobial agents and acid-lowering drugs.[8] Because patients can be reinfected from environmental sources (such as water) in tropical countries, it is not always possible to permanently eradicate the infection in all persons.[9, 9a] For this reason there is currently much interest in the development of an oral vaccine to prevent new infections.

THE ORGANISM, ITS MICROBIOLOGY AND TAXONOMY

H. pylori is the type strain of a new genus of bacteria named *Helicobacter* because of the helical or corkscrew shape of these organisms. Their morphology and sheathed flagella may facilitate their motility in the mucous layer of the gastrointestinal tract. *H. pylori* is microaerophilic, which means that it prefers a reduced amount of oxygen for growth, but is not anaerobic. This is probably the environment found in the mucous layer of the gut, a transitional zone between the anaerobic lumen and the oxygenated mucosa. The characteristics and growth requirements of *H. pylori* are listed next.

Morphologically, *H. pylori* is a gram-negative spiral, 3.5 μm long × 0.6 μm thick, with 1.5 wavelengths and four to seven sheathed flagella at one end of the organism, as shown in Figure 29–1. In tissues *H. pylori* appears spiral and lies close to the gastric mucous epithelial cells and in the mucous glands. Squashed or smeared fresh gastric biopsy specimens may be stained by Gram's stain, or examined by phase contrast microscopy.[10, 11] In histologic sections *H. pylori* stains well with Giemsa, toluidine blue, or silver stains. Hematoxylin and eosin (H&E) stain does not adequately demonstrate *H. pylori.*

In culture, *H. pylori* appears longer and spiral forms are not as obvious. Usually comma shapes and U shapes (unseparated dividing organisms) are seen.[12]

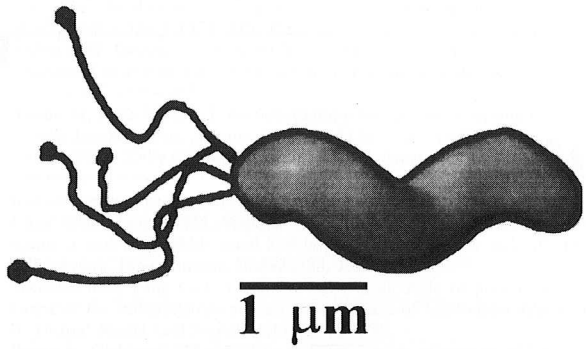

Figure 29–1 *Helicobacter pylori* (3.5 × 0.6 μm) has a smooth wall and four to seven sheathed flagella arising from only one end of the cell. These features distinguish it from *Campylobacter* spp., which have rough cell walls and a single, thinner, unsheathed flagellum at each end of the cell. Other *Helicobacter* spp. have distinguishing features such as many flagella and axial filaments (*H. felis* from cats) or flagella sprouting from the sides of the organism (*H. mustelae* from ferrets). Mature organisms appear as spiral forms with 1.5 wavelengths.

Culture

H. pylori is microaerophilic, growing in reduced O_2 at 37°C in 4 to 6 days on fresh (moist) chocolate or blood agar. The "*Campylobacter* atmosphere" generated by a commercial *Campylobacter* kit in a gas jar provides an excellent atmosphere for *H. pylori* culture. If available, a 5% CO_2 incubator also provides excellent growth conditions. If nothing else is available, a candle jar with moist paper towels in the bottom will provide an adequate atmosphere, and even gas-generating methods such as the "steel wool and Alka Seltzer" idea of Pennie et al.[13] can be used.

Selective Media

Although *H. pylori* can be isolated easily from gastric biopsy samples onto nonselective media, occasional patients have bacterial contamination of the biopsy, and overgrowth of commensal flora will make isolation of *H. pylori* difficult. To maximize the isolation rate, a selective medium can be made by adding vancomycin, trimethoprim, and amphotericin to the culture medium.[14] Special selective media for *H. pylori* culture are available,[15] or *Campylobacter* isolation media such as Skirrow's medium may also be used.[16]

Identification

On blood or chocolate agar, transparent or pale-yellow 1- to 2-mm "water spray" colonies appear after 3 to 6 days. They are strongly positive for catalase, oxidase, and rapid urease. In the last-named test, a pink color is observed within 5 minutes of applying a colony to Christensen's urea agar. The organism may also be grown in broth such as shaking tubes of *Brucella* broth[18] or in gas-permeable shaking bags[19] in a CO_2 incubator, or in fermenters.[20]

Pitfalls

When subculturing *H. pylori*, one should always examine the Gram's stain morphology of *H. pylori* as well as perform the biochemical identification tests described earlier. Contaminating organisms may appear similar to the naked eye and are often urease-, oxidase-, or catalase-positive.

EPIDEMIOLOGY AND TRANSMISSION

H. pylori infects more than 70% of persons in most developing countries and about 30% of persons in developed countries where it is far less common in younger persons. In societies which have recently emerged to affluence (such as Japan), *H. pylori* is still quite common and infects most persons over the age of 40 years.

Most studies show that *H. pylori* is acquired in childhood, probably by the fecal-oral route. The bacterium has been isolated from the feces of children in The Gambia[21] and polymerase chain reaction (PCR) techniques have demonstrated the genome of the organism in drinking water from Peru.[22] In developing countries, children may be infected at the rate of 15% to 20% per annum so that most of the population is infected by adulthood. The initial infection with *H. pylori* may be somewhat precarious in that some children lose the infection spontaneously for a time but then reacquire it from the environment. This may occur several times before the child maintains a stable permanent gastric infection.[23] Initially the infection may spread from one parent to one of the children in the family, then spread to other family members, siblings, or the uninfected parent, individually or severally, by fecal contamination or perhaps vomitus.[24] Thus the infection is transmitted from one generation to the next, but young children appear to amplify the infection rate.

The exact mechanism of spread is still somewhat controversial. *H. pylori* DNA is present in the dental plaque of some infected persons[25] suggesting that oral-oral spread could occur from actions such as kissing. *H. pylori* has been cultured from gastric juice so reflux of gastric juice, which often occurs, could deliver infectious organisms in the mouth. Thus oral-oral spread of *H. pylori* seems inevitable but has been hard to demonstrate. For example, in Belgium, investigators studied infants born to 67 infected mothers but could detect only one new *H. pylori* infection by breath test during a 12-month period.[26] This may mean that most new infections in developing countries come from other children, other relatives, or environmental sources. The prevalence rate in developing countries, as compared with Western countries, is shown in Figure 29–2.

PATHOGENESIS

Acute Achlorhydric Gastritis

Almost 100 years ago, William Osler described acute *H. pylori* infection as a pediatric vomiting illness[27] which he termed "gastritis with achlorhydria." As *H. pylori* became less common in Western countries, the syndrome was forgotten and was omitted from the medical texts after

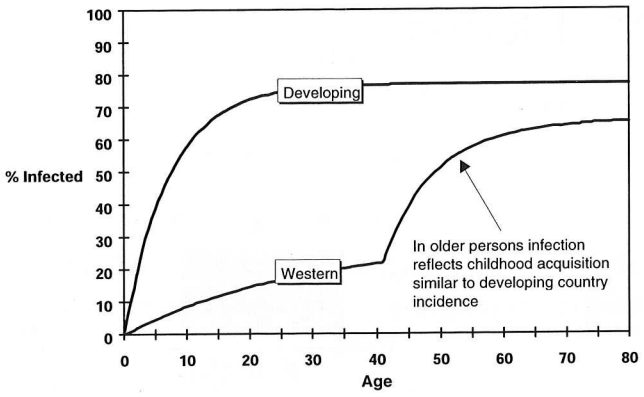

Figure 29–2 The prevalence of *Helicobacter pylori* in developing and Western countries. In developed countries, *H. pylori* is decreasing in prevalence so that most of the infections are in those over the age of 50 years who likely acquired the infection during childhood. The infection in young persons is only seen in immigrants from high-risk countries.

1960. In some research laboratories, however, groups of volunteers were inadvertently infected with *H. pylori* after contaminated gastric tubes were shared among subjects.[28, 29] These miniepidemics have provided us with knowledge of the clinical syndrome associated with acute *H. pylori* infection. In the largest of the published epidemics, 21 subjects developed gastritis with pentagastrin-fast achlorhydria lasting several weeks.[29] In addition, all cases that were followed 10 years later were still infected.[30] In addition to the accidental epidemics, cases of endoscopic infection with *H. pylori*[31, 32] and even deliberate self-ingestion experiments[33, 34] have added to our knowledge. Most of the well-studied acute cases were observed in adults, but occasional pediatric cases have also been reported, confirmed by rising antibody titers following an acute gastrointestinal illness.[35] In the acute *H. pylori* infection, symptoms begin about 72 hours after ingestion of the organism. Gastric acid secretions may initially increase, associated with varying degrees of epigastric discomfort[34] and, at the end of the first week, vomiting episodes.[32, 33] Symptoms may only last a few days and then resolve as the bacterium induces achlorhydria. The cause of the achlorhydria is unknown but could possibly be secondary to the action of a bacterial toxin[36] or to generation of ammonia by urease.[37]

Immediately after ingestion by a healthy person, it is thought that the urease enzyme of *H. pylori* enables the bacterium to survive in acid by generating ammonia and bicarbonate from urea present in the gastric juice[38]:

$$\begin{array}{l} NH_2 \\ | \\ C=O + 2H_2O + H^+ \xrightarrow{\text{urease}} 2NH_4^+ + HCO_3^- + H_2O \\ | \\ NH_2 \end{array}$$

Urease is discussed later under Diagnosis.

Since the acute infection is associated with weeks, months, or even years of reduced gastric acidity, *H. pylori* may increase susceptibility to other ingested enteric pathogens and thus be an important pathogen in the pediatric age group.[39]

Attachment

H. pylori has several attachment mechanisms that enable it to selectively colonize gastric mucosa but not intestinal mucosa. To various degrees, *H. pylori* is adherent to Lewis B antigen,[40] phosphatidylethanolamine,[42] and ganglioside GM_3,[43] all of which are present on the gastric mucous epithelial cells. In addition, *H. pylori* synthesizes Lewis X antigen.[41] Once attached, *H. pylori* induces the production of interleukin-8 (IL-8) which in turn attracts neutrophils.[44]

Cytotoxins

Leunk et al.[45] were the first to observe that supernatants of *H. pylori* could induce vacuolation in cultured epithelial cells. Further studies by Cover et al.[46] showed that the effect was marked by a 127-kD antigen termed *cytotoxin-associated antigen A (CagA).* Interest heightened when patients with duodenal ulcer were found to almost always have the CagA antigen[47] whereas only 60% of patients without ulcer had the antigen. CagA was also unusual in that it was completely absent from *H. pylori* isolates that did not produce cytotoxic effects. Ultimately it was discovered that CagA was a marker for the actual toxin, subsequently called vacuolating toxin A (VacA).

It is actually the cytotoxin (VacA) that causes vacuoles to form in the epithelial cells.[48] All *H. pylori* have a *vacA* gene which codes for cytotoxin, but the exact sequence of the *vacA* gene varies, so that not all VacA protein products are the same, and some are relatively less cytotoxic in vitro. Atherton et al.[49] noted that there were two *vacA* gene subunits, which the authors termed "s" and "m." Each of these could exist in two forms, "s1/s2" and "m1/m2." Only the s1-m1 and s1-m2 subtypes were associated with the active cytotoxin or with duodenal ulcer (Fig. 29–3).

With few exceptions, the virulent form of the *vacA* gene (which encodes a vacuolating cytotoxin) is only present when the *cagA* gene is present, as marked in patients by the presence of antibodies to CagA protein (even though the precise biologic role of the protein is not clear at present). Thus CagA protein production (and antibody to CagA) is a marker for strains of *H. pylori*, which may be more likely to be associated with duodenal ulcer or gastric cancer. The exact mechanisms whereby these proteins are related to various diseases are presently unclear.

DISEASE ASSOCIATIONS AND CLINICAL MANIFESTATIONS

Active Chronic Gastritis

Chronic gastritis refers to the presence on histologic study of mononuclear cells (lymphocytes and plasma cells) in the gastric mucosa.[2] Histologic chronic gastritis

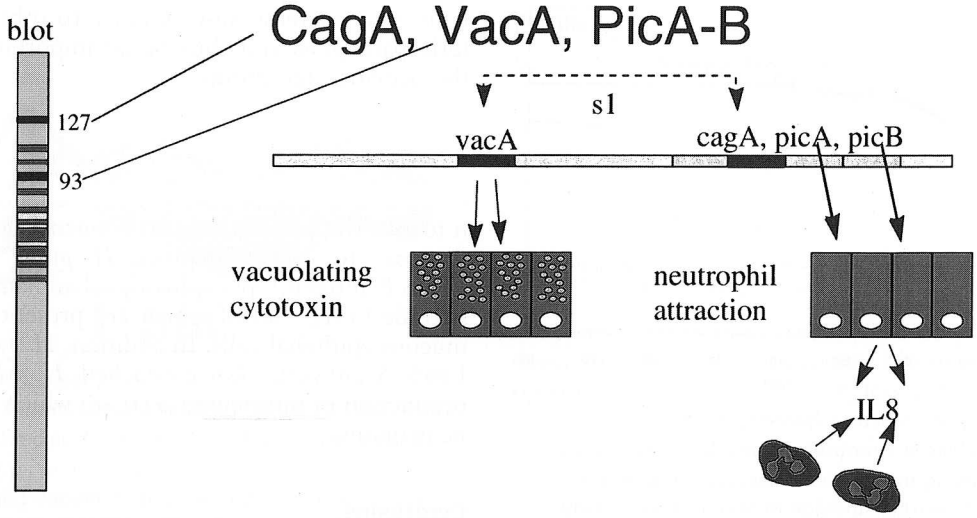

Figure 29–3 Relationships of cytotoxin genes and proteins. The left side diagramatically shows a representative immunoblot pattern of a patient with a duodenal ulcer and *Helicobacter pylori* infection. The 127-kDa band is the cytotoxin-associated gene A (*cagA*) product. The cagA pathogenicity island has a higher guanine + cytosine content than the rest of the *H. pylori* genome. This suggests that the *cagA* gene group has long ago been imported from a different genus. The *vacA* (vacuolating toxin A) gene has two main subunits (s and m), and these can each be in two subtypes (s1, s2, and m1, m2). When s2 is present, the cytotoxic potential of the organism is very weak and is not usually associated with peptic ulcer, and the CagA island is usually absent. PicA-B, permits induction of cytokines.

is associated very closely with *H. pylori* and there are few patients with this finding who do not have the organism.[50] There is also a variable amount of neutrophilic infiltration of the mucosa, typically with neutrophils invading the neck of a mucous gland. This latter appearance gives the name "active" or "acute" to the typical histologic appearance called active chronic gastritis.[1] Because the cause of chronic gastritis was unknown before the discovery of *H. pylori*, the terminology was confusing and nonstandardized. In most of the literature, terms such as "atrophic gastritis," "superficial gastritis," "simple gastritis," "antral gastritis," and "type 1 gastritis" all refer to the histology of *H. pylori* infection. The various classifying and descriptive terms for the lesion have been well described in several papers.[51, 52, 52a]

In the antrum of the stomach *H. pylori* is most numerous on the surface of the epithelium (beneath the mucous layer) but it also lives in the mucus-secreting glands. In the body of the stomach (corpus), the organisms are found on the surface of the mucosa but do not usually colonize the acid-secreting glands to a major degree. The inflammation tends to collect near the bacteria. Thus in the corpus, the appearance is quite compatible with a "superficial gastritis," whereas in the antrum, the inflammation often reaches the muscularis layer. In either place the lesion can be associated with lymphoid follicles. Attachment of the bacterium to the epithelial cells causes damage to the cytoskeleton of the cells so that they bulge out rather than maintain a healthy flat luminal surface. Under periodic acid–Schiff staining, the mucus content of infected gastric mucosa is far less than normal and cells are shorter with deficient apical mucus content. These changes have been termed the destructive mucin lesion of the covering gastric epithelium.[52a, 53] Lymphocytic infiltration in the deep portion of the gland is termed *chronic active gastritis*. Cytotoxic lymphocytes are postulated to be sensitized to the glands, which may be destroyed and result in intestinal metaplasia or chronic atrophic gastritis.[9a]

Over the lifetime of the infected person, active chronic gastritis may damage the mucosa so that inflammation replaces glandular elements (atrophy) and intestinal cells replace gastric mucus-secreting epithelium (intestinal metaplasia). The lesion of atrophic gastritis has both these elements and may be the final "burned out" phase of *H. pylori* infection, usually seen in older persons. In tropical countries, however, where *H. pylori* may have been present from a very early age, this lesion may be seen also in young adults and is believed to be a risk factor for gastric cancer.[52b]

Duodenal and Gastric Ulcer

The most obvious disease associated with *H. pylori* is peptic ulceration (Fig. 29–4). More than 90% of duodenal ulcers are associated with *H. pylori*.[54] When a patient with a duodenal ulcer does not have *H. pylori* infection, etiologic factors such as Zollinger-Ellison syndrome or nonsteroidal anti-inflammatory drug (NSAID) use are likely.[55]

In gastric ulcer, two causes prevail, and many patients will exhibit both. Most gastric ulcers have *H. pylori* and these can be identified by presence of the bacterium or chronic gastritis. The stomach is also directly exposed to ingested agents such as an NSAID and is more likely than the duodenum to ulcerate in response to these agents. Therefore, in the United States, about 35% of

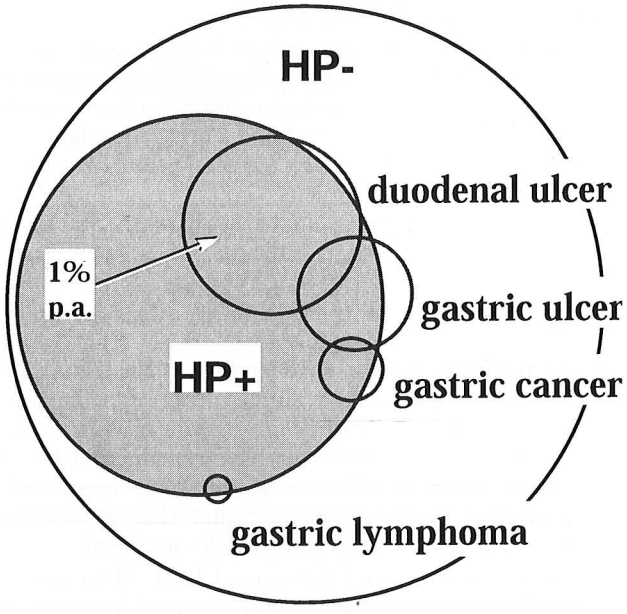

Figure 29–4 Disease associations with *Helicobacter pylori* (HP). The large circle represents a typical population in a developed country where 60% of persons are *not* infected with *H. pylori*. The darker circle represents the 40% of persons who *are* infected with *H. pylori*. Even so, nearly all the duodenal ulcers and gastric ulcers occur in the *H. pylori*–positive group. Each year, 1% of infected patients undergo transition from asymptomatic gastritis to symptomatic peptic ulcer. Note that most gastric adenocarcinomas and gastric mucosa–associated lymphoid tissue (B-cell) lymphomas also occur in the *H. pylori*–positive persons. Controversy reigns as to the role of *H. pylori* in persons with dyspepsia but in whom ulcers are not found: should *H. pylori* be treated in these persons, or ignored?

gastric ulcers are not associated with histologic chronic gastritis or *H. pylori* but are caused by NSAIDs.[52]

In tropical countries where NSAIDs are less widely used and *H. pylori* is very common, most gastric ulcers are caused by *H. pylori*.[57] In tropical countries also, gastric ulcers are often malignant and require endoscopy and biopsy for histologic examination.

The proposed causation of duodenal ulcer is as follows. Persons with *H. pylori*, but with colonization mainly in the antrum, have robust acid secretion and a defective mucosal barrier in the pyloroduodenal region. Inflammation in the antrum impairs the growth of D cells (which make somatostatin) and thus decreases their inhibitory effects on the gastrin-producing G cells. This results in a relative increase in gastrin production which may in turn, over the lifetime of the patient, cause a hyperplasia of the acid-secreting mucosa. In the presence of normal or raised acid secretion, gastric mucous cells are more commonly present in the duodenal bulb and are colonized with *H. pylori*, seeded from the infection present in the antrum. This causes neutrophil invasion of the duodenal epithelium (duodenitis) and susceptibility to ulceration. Inflammation is more severe when the *H. pylori* secretes CagA, thus associating the cytotoxin with duodenal ulcer.[58, 59]

The different locations of gastric ulcer and duodenal ulcer may be the result of variations in the aforementioned factors. Slightly lower than normal acid secretion is typical of gastric ulcer patients. Infection at a younger age (see also Gastric Cancer section) may cause more parietal cell damage and a lower acid secretion in adulthood. In patients who develop or are born without gastric mucous cell metaplasia in the duodenum, colonization cannot occur beyond the pylorus, so duodenitis does not develop and the prerequisite lesion for duodenal ulcer is absent.

Presently, it is accepted that *H. pylori* is the most important etiologic factor in peptic ulcer disease and that all persons with peptic ulcer should be tested for the bacterium and treated with antimicrobial agents when evidence of the infection exists.[8, 60] In many studies, recurrence rates were less than 10% when *H. pylori* was eradicated, whereas more than 90% of ulcers recurred when the bacterium persisted.[61] Thus, most patients are cured of their ulcer disease with effective antibiotic treatment.[62]

Gastric Cancer

Adenocarcinoma

Worldwide, gastric cancer is the second most common cancer, the high prevalence areas being Brazil, Colombia, Korea, China, and Japan. *H. pylori* infection affects more than half the population in these countries.[63] The incidence of gastric cancer has declined in the United States since 1930. At that time it was the most common cancer, but now it ranks about ninth.[64]

In an extensive review of gastric cancer and *H. pylori*, the Eurogast Study Group[63] determined that presence of *H. pylori* confers an approximately sixfold risk of gastric cancer, accounting for about half of all gastric cancers. Thus, in most tropical countries where *H. pylori* is prevalent, gastric cancer is also common. In India, Bangladesh, the Middle East, southern China and some African countries, however, *H. pylori* is prevalent but gastric cancer is not. This paradox suggests that genetic, dietary, and other unknown environmental factors are also important in the causation of adenocarcinoma.[65, 65a]

The proposed chain of events in gastric carcinoma starts with a very early (age 1 to 5 years) infection with *H. pylori* so that the corpus mucosa is damaged during childhood and when adulthood is reached there is inadequate acid secretion. In this setting, ulcers are unlikely but a larger surface area of the stomach is involved in the process. Some damaged areas change to intestinal metaplasia, and chronic atrophic gastritis and defective acid secretion eventually allow other organisms to colonize the stomach.[66–68] In this setting, nitrates can be changed to nitrites and then to nitrosamines, which are carcinogenic. In addition, inflammation itself can cause nitrosamines to form in the mucosa. Inflammation is more severe when the *H. pylori* secretes CagA, thus associating the cytotoxin with gastric cancer.

The Ulcer-Cancer Controversy

This subject has been reviewed by Parsonnet.[69] Examination of patients with duodenal ulcer reveals that they

commonly have high gastric acid secretion and an *H. pylori* organism that secretes CagA.[70] Recent studies on patients with gastric cancer have also shown high rates of CagA-positive *H. pylori* infection.[71] The controversy exists because gastric acidity is usually low in cancer patients but high in duodenal ulcer patients. Both have CagA but gastric cancer appears to be less common in (high acid) duodenal ulcer patients.

One proposed explanation for this is the time of acquisition of the infection. In a tropical country where *H. pylori* is acquired in early childhood, the gastric mucosa is damaged so that adult levels of high acid secretion may never be achieved after puberty. Thus, even if CagA is present, the patient may never develop a duodenal ulcer, but is susceptible to later gastric cancer.[7a,b] Furthermore, in tropical areas the prevalence of gastric metaplasia in the duodenum may be lower than that in developed areas.[71c]

If *H. pylori* is acquired in later childhood or in the adult years (as in Western countries), then acid secretion is already high and the infection tends to affect mainly the antrum of the stomach, leaving the acid-secreting part of the stomach (the corpus) intact. High acid secretion is possible and allows the expression of duodenal ulcer disease.

Lymphoma

In the initial report of the Eurocast Study Group, Wotherspoon et al.[72] found that 92% of 110 mucosa-associated lymphoid tissue (MALT) lymphomas were associated with *H. pylori* compared with 50% of control cases. Subsequent reports suggest that these tumors are sometimes driven by continuing *H. pylori* antigenic stimulus and regress when *H. pylori* infection is treated.[73, 74] The German MALT-Lymphoma Study Group[75] reported that apparent cure of MALT lymphoma occurred in half the patients in whom *H. pylori* was eradicated. It is now widely accepted that *H. pylori* eradication therapy should be the initial step in the treatment of proven or suspected gastric lymphoma.

DIAGNOSIS

The diagnosis of *H. pylori* may be by invasive or noninvasive methods, or both, as shown in Table 29–1. Invasive methods usually mean endoscopic biopsy of gastric mucosa, although they can include blind biopsy, nasogastric aspiration, or the gastric string test.[76] Noninvasive tests are primarily serologic tests that detect antibody to *H. pylori*, and urea breath tests.

Invasive Tests

Histology

At endoscopy biopsies are taken for histologic study from intact mucosa that is away from any local lesion. This allows the pathologist to separate true inflammation (active chronic gastritis) from changes due to acute ulcer healing. Biopsies for *H. pylori* should be separate from biopsies taken to exclude malignancy, which of course need to be taken from the lesion or ulcer border. At least two or, preferably, three biopsies need to be taken to detect *H. pylori* histologically. On the greater curve one biopsy can be taken from the antrum and one from the midcorpus. On the lesser curve one should be taken from the angular notch.[77] In addition to routine H&E sections, the specimens should be stained with Giemsa or a silver stain such as Warthin-Starry or Genta stain.[78]

Culture

Culture methods have been described earlier. Cultures may be moistened with a single drop of saline and transported to the laboratory in a sterile tube the same day. In some studies organisms have remained viable in snap frozen biopsies. This method allows later study of the original bacterial isolate rather than a passaged organism, but risks losing some viable organisms.

Culture has also been performed from blind gastric mucosal biopsies, from gastric aspirates, and from gastric string tests. These methods are less sensitive than culture of biopsies and are not widely used. Biopsy material, gastric mucus, and gastric juice can, of course, also be examined with polymerase chain reaction (PCR) or immunologic methods to detect *H. pylori*, but at present these are not reproducible in different laboratories and have no particular advantage over culture or histology.

Urease Test

The ability of *H. pylori* to produce urease allows one to rapidly detect the organism in gastric biopsy material. Typically, the mucosal biopsy specimen is placed in a medium containing urea and phenol red, and lightly buffered to a pH of 6.0 to give a yellow color at baseline. If urease (or *H. pylori*) is present, urea is converted to ammonia and the pH rises with a subsequent color change from yellow to red. The medium should also contain a bacteriostat so that bacterial growth with urease-producing organisms does not occur and only preformed bacterial urease is detected.[79] *H. pylori* is a prolific urease producer so that the reaction occurs in a few minutes in biopsies from infected patients. This test has superseded Gram's stain and even histology in some laboratories. Since the test is so specific for *H. pylori*, once a positive urease test has been noted, other diagnostic material is often unnecessary and may be discarded to save expense.[80]

Noninvasive Tests

Infection is almost always accompanied by a rise in specific IgG antibody to *H. pylori*. IgM is present in some persons during the acute infection but has not been well studied because acute infections are rarely documented. IgA is present in 80% of persons with *H. pylori* so it can be used to diagnose the infection when present, but the absence of IgA does not exclude infection. Thus, in most cases, IgG is the best predictor of *H. pylori* infection (Fig. 29–5).

Tests to detect IgG come as a laboratory-based

Table 29–1 Accuracy of Diagnostic Tests for *Helicobacter pylori* Infection in 268 Patients Undergoing Esophagogastroduodenoscopy

Tests	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Invasive				
Biopsy: Chronic inflammation*	100	66.3	84.4	100
Biopsy: Acute inflammation†	86.7	93.7	96.2	79.5
Biopsy: Warthin-Starry silver stain‡	93.1	99.0	99.4	88.7
CLOtest rapid urease test§	89.6	100	100	84.1
Noninvasive				
^{13}C-urea breath test‖	90.2	95.8	97.5	84.3
Serum IgG¶	91.3	91.6	95.2	85.3
Serum IgA¶	71.1	85.3	89.8	61.8

*Chronic inflammation present in gastric antral biopsies.
†Acute inflammation present in gastric antral biopsies.
‡Warthin-Starry stain of gastric antral biopsy.
§Urease test conducted on gastric antral biopsy with results ascertained at 24 hours.
‖^{13}C-urea breath test 60 minutes after administration of 150 mg ^{13}C-labeled urea.
¶Serum antibodies to *H. pylori*.
Data from Cutler AF, Havstad S, Ma CK, et al: Accuracy of invasive and noninvasive tests to diagnose *Helicobacter pylori* infection. Gastroenterology 109:136–141, 1995.

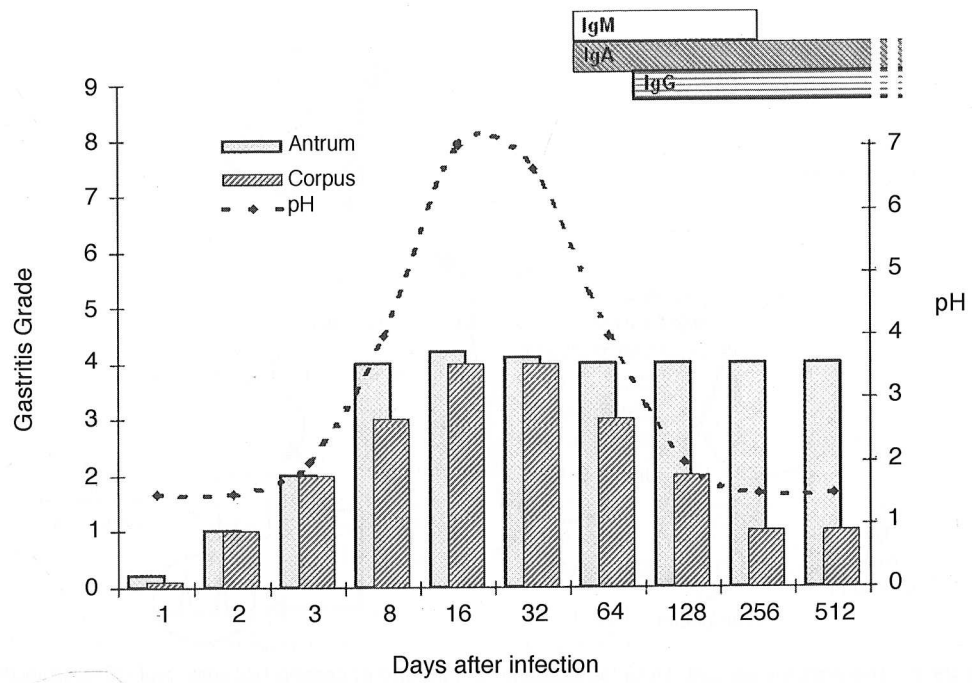

Figure 29–5 The natural history of *Helicobacter pylori* infection. The horizontal axis shows the time scale in days over 18 months. The left vertical axis is gastritis grade as represented in the columns showing antral and corpus mucosa inflammation graded 0 to 4. The right vertical axis shows the pH of gastric juice on a scale of 0 to 7. Note that corpus mucosa inflammation (hatched vertical bars) subsides after 3 months, whereas antral inflammation remains. As the corpus mucosa returns to near normal, acid secretion revives and gastric pH (dotted line) falls to normal acidic levels. Variable early responses are seen in IgA and IgM. IgG is present after the fourth week and remains as the most stable antibody response in nearly all infected persons.

multiwell enzyme-linked immunosorbent assay (ELISA) kit, which is the most accurate serologic test. In properly selected patients, sensitivity and specificity both exceed 95%. In patients who have been treated for *H. pylori* infection in the preceding 2 years, IgG may remain positive and give an incorrect result in persons who no longer have *H. pylori* infection.[81] For this reason the urea breath test is a better choice for follow-up and in patients with a history of antibiotic use for reasons other than *H. pylori* infection.

As well as being present in blood, small amounts of IgG may be detected in urine and gingival secretions. The latter two sources allow diagnosis from urine specimens and saliva but these tests are experimental at present.

Urea Breath Tests

The prolific urease production of *H. pylori* also allows it to be detected by means of the urea breath test. The test is highly specific for *H. pylori* because there is usually no other source of active gastric urease in the stomach. Mammalian cells do not produce urease,[82] and urease swallowed from bacterial sources in the oropharynx is immediately denatured by gastric acid.[83]

In the urea breath test, fasting patients are given a trace of either ^{14}C-urea (1 μCi) or ^{13}C-urea (100 mg). If *H. pylori* is present in the stomach, the urea is hydrolyzed to CO_2 and NH_4^+ (as shown in Fig. 29–6). Many variations on the test have been described.

^{14}C-Urea Breath Test

In the most recent version of the ^{14}C-urea breath test, developed at the University of Virginia, the isotope is enclosed in a quick-dissolve capsule. The potential advantage of this is that urea is no longer exposed to the bacterial flora of the mouth during ingestion. Therefore, urea hydrolysis only occurs if urease (*H. pylori*) is present in the stomach. Since *H. pylori*–negative subjects have near-background levels of ^{14}C in the breath, the difference between *H. pylori*–negative and *H. pylori*–positive is comparatively greater than with liquid-based (urea solution) tests. This allows a lower dose of urea to be used (1 μCi) and diagnosis with a single breath sample at an earlier time point. Samples collected in balloons are quite stable and can be mailed to a centralized testing facility.

Other ^{14}C-urea tests have been described in which a meal is administered. This does not seem necessary because so little physical urea is used (less than 1 μg). Therefore, the reaction time is quite short.

^{13}C-Urea Breath Test

The ^{13}C-urea breath test utilizes a high calorie meal to hold isotope in the stomach long enough for the urea

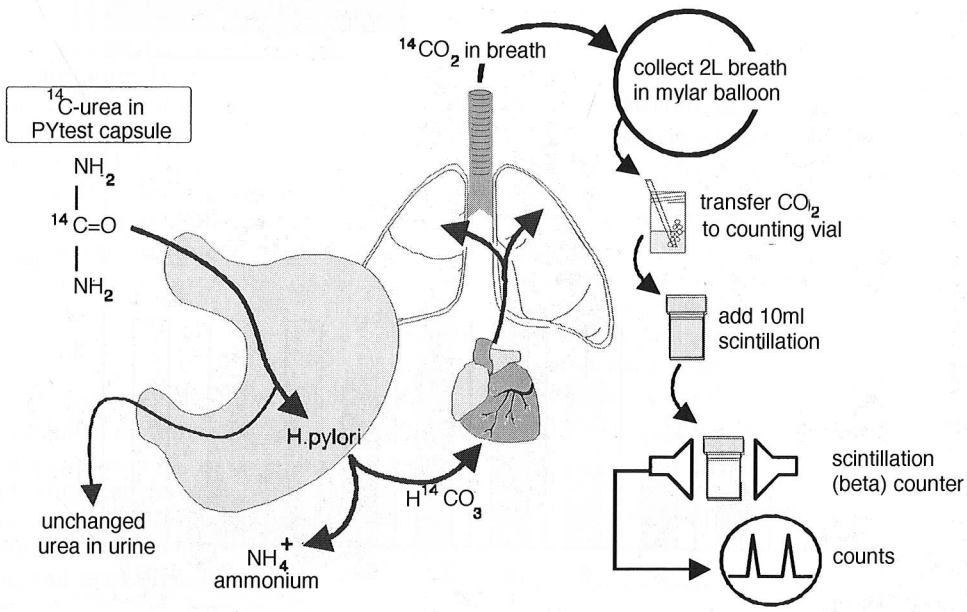

Figure 29–6 The urea breath test. Urea labeled with an isotope of carbon (a capsule of ^{14}C-urea in this illustration) is swallowed by the fasted patient. Ten to 15 minutes later, a breath sample is collected into a balloon, processed as shown, then counted in a scintillation counter. $^{14}CO_2$ can be detected in the breath of a patient infected with *Helicobacter pylori*. When *H. pylori* is not present, the urea remains intact and there is no $^{14}CO_2$ in the breath. Unchanged ^{14}C-urea is excreted in the urine. Since more than 90% of the isotope is excreted within 3 days, radiation exposure is exceedingly small, about the same as natural background in 24 hours (0.3 mrem). In the ^{13}C-urea breath test the patient first swallows a high-fat meal or drink which serves to delay gastric emptying. Ten minutes later a baseline breath sample is collected and a solution of isotope is swallowed. Diagnostic breath samples are collected 20 to 40 minutes later. Breath samples are analyzed in an isotope ratio mass spectrometer.

hydrolysis reaction to occur. This maneuver is necessary for the ^{13}C-urea breath test because about 75 to 125 mg of urea is required and this much urea, when dissolved in gastric contents, exceeds the K_m of the urease enzyme.[84] Thus, at the very least, 20 minutes must elapse before diagnostic samples can be taken. Besides the delay, a second drawback to this method is that the meal prevents endoscopy being done on the same day as the test.

Another difficulty is caused by the fact that ^{13}C is abundant in nature, being 1.1% ± 0.15% of natural carbon. However, the ^{13}C content is much higher in some food (corn syrup) so individuals can have variations in the percentage of expired ^{13}C. This means that a baseline breath sample must be taken[85] before the test begins so that an *increase* in ^{13}C concentration can be measured. It also means that single-sample ^{13}C breath tests are an impossibility. However, some prefer the use of this nonradioactive method (where available) in children.

Diagnostic Criteria for Research Studies

Table 29–1 gives comparative data on the accuracy of various diagnostic tests as observed by Cutler et al.[86] Although histology appears accurate, these data reflect the results obtained by an expert pathologist with considerable experience in *H. pylori* diagnosis. Accuracy is quite variable among community pathologists, depending on their experience and the technical excellence of the staining methods used.

For clinical research, concordance between two different methods is necessary to prove the presence or absence of *H. pylori.* Good combinations for initial diagnosis would be histology and culture, urease test and culture, histology and serology, or urease test and serology.

Proof of cure requires demonstration of sterile gastric mucosa, by two tests, 4 weeks after completion of therapy. Alternatively, two negative breath tests will suffice, the first at 4 weeks post therapy and the second at 6 to 8 weeks post therapy.

TREATMENT

What is the role of treatment of *H. pylori* infection in the tropics? In many ways treatment is similar to that in the United States where eradication is prescribed for patients with peptic ulcer disease and in the unusual patient with gastric lymphoma.

In the tropics, regimens containing metronidazole are much less effective than those in which metronidazole is replaced by another drug useful against *H. pylori.* An example is the observation that in a Bangladeshi population in London, almost all isolates of *H. pylori* were resistant to metronidazole.[87] For example, in one study furazolidone replaced metronidazole in a 10-day regimen that also included bismuth subsalicylate and amoxicillin and the efficacy of eradication increased from 49% to 79%. Second, in Peru, studies strongly suggest that in poor populations there is rapid recurrence even after successful eradication of *H. pylori* from the stomach. *Eradication* is defined as the absence of *H. pylori* at least 4 weeks after the last dose of antimicrobial therapy was given.[9a] Using this definition, recurrence can either be due to the failure to eliminate the bacteria from the stomach or to a new infection. At present it is not clear which of these two conditions is responsible for recurrence. Failure to clear the bacteria most likely would not be different in developed and developing countries since it will depend on host response. In contrast, rapid reinfection is most likely because fecal contamination via contaminated water or food will occur much more rapidly in developing areas.

Keeping the foregoing issues in mind, therapy for *H. pylori* infection usually involves at least two agents. Typically, treatment consists of bismuth with two antibiotics; or an acid-reducing drug (proton pump inhibitor) with one or two antibiotics. This is because *H. pylori* quickly develops resistance to metronidazole and macrolides,[88, 89] and may be protected by gastric acid, which inactivates some agents.[90]

Therapy needs to be given for at least 7 days and not more than 14 days. Thus a therapeutic cycle for *H. pylori* infection would take 6 weeks starting with 2 weeks of therapy, followed by 4 weeks without therapy, with a follow-up breath test at the end of the sixth week. If *H. pylori* is still present, then a second course of therapy might be given, using different antibiotics than were used in the first therapy. The first satisfactory successful therapy for *H. pylori* infection was the combination of bismuth, tetracycline, and metronidazole.[91] This triple therapy gives a cure rate of 90% in persons with organisms sensitive to metronidazole and a 50% cure rate when *H. pylori* is resistant to metronidazole. This inexpensive therapy is a good first choice when more than 70% of isolates are sensitive to metronidazole. By adding an acid-lowering agent, such as ranitidine or omeprazole, the cure rate with the triple therapy exceeds 95% in sensitive strains.[92]

In the tropics, since *H. pylori* is frequently resistant to metronidazole, an alternative agent should be used in drug combinations. The ideal choice is clarithromycin which gives cure rates of 85% to 95% in combination with omeprazole and amoxicillin.

As mentioned previously, furazolidone is an inexpensive alternative to metronidazole, but cure rates are less than with clarithromycin. A list of well-studied therapies is given in Table 29–2.

PREVENTION AND CONTROL

The rapid recurrence of *H. pylori* infection in some areas means that its treatment in impoverished tropical areas needs to be based on objectives that have a likelihood of some success. Goals for control of infection will have to be tempered with the additional need for improved sanitation. Thus, for example, antimicrobial treatment of the majority of the world's population living in tropical, developing areas to eradicate *H. pylori* for the purpose of preventing cancer would be unrealistic at present. On the other hand, prevention of gastric ulcer and duodenal ulcer recurrence for periods of a year or two might have some utility.

Table 29–2 Effectiveness of Common Therapies, Highest to Lowest

Clarithromycin 1.0 g/day	Amoxicillin 2.0 g/day	Omeprazole 20 mg bid	85%–90%
Metronidazole 1.0 g/day	Clarithromycin 1.0 g/day	Omeprazole 20 mg bid	80%–95%
Metronidazole 1.0 g/day	Amoxicillin 2.0 g/day	Omeprazole 20 mg bid	80%–90%
Metronidazole 1.0 g/day	Tetracycline 2.0 g/day	Bismuth subsalicylate or bismuth subcitrate	80%–90%
	Clarithromycin 1.5 g/day	Ranitidine-bismuth-citrate	80%–90%
	Clarithromycin 1.5 g/day	Omeprazole 20 mg bid	80%–90%
Metronidazole 1.0 g/day	Furazolidone 100 mg qid	Bismuth subsalicylate	65%–75%
Metronidazole 1.0 g/day	Amoxicillin 2.0 g/day		70%–75%
Metronidazole 1.0 g/day		Bismuth subsalicylate or bismuth subcitrate	65%–75%
		Bismuth (liquid De-Nol)	20%–40%
	Clarithromycin 1.5 g/day		20%–40%
	Amoxicillin 2.0 g/day		10%–20%
Metronidazole 1.0 g/day			1%

The role that treatment will have in reversing the progress of precancerous lesions to cancer is not known. Evidence suggests that treatment may reverse dysplasia but not intestinal metaplasia. In patients with severe intestinal metaplasia associated with atypical changes or dysplasia, it is probably worthwhile at present to attempt to eradicate *H. pylori* from the mucosa. In patients with gastric lymphoma, a condition seen more commonly in developed countries, eradication is mandatory because tumor regression occurs when *H. pylori* infection is treated. There is no evidence to date, however, that eradicating *H. pylori* in patients with gastric cancer will affect the course.

The rapid recurrence of *H. pylori* infection in treated patients makes vaccine use in this population highly attractive. Urease vaccines that protect mice are now being tested in phase 1 studies. These vaccines will not only have to be safe but will also need to work in children because of early infection if they are to protect against ulcer disease and the development of gastric cancer. Another possible use for the vaccine will be to prevent recurrence of *H. pylori* infection after effective antimicrobial therapy.

It is clear that *H. pylori* infection is one of the most common infections in the tropics, with significant association with peptic ulcer disease, gastric cancer, and possibly with other enteric infections. New diagnostic, therapeutic, and preventive measures will undoubtedly determine the evolving approaches to better controlling the consequences of *H. pylori* infections worldwide.

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