A BACTERIAL CARCINOGEN:  
**HELCOBACTER PYLORI**

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A BACTERIAL CARCINOGEN – HELICOBACTER PYLORI

COURSE OBJECTIVES
Upon completion of this course the participant will be able to

- Describe the principal characteristics of Helicobacter pylori and its habitat
- Outline methods of isolation and identification
- Explain the role of H. pylori in human disease
- List suggested treatment protocol
- Describe virulence factors and discuss host response to infection
- List diagnostic methods currently in use
- Explain the epidemiology of infection in underdeveloped and in developed countries
- Discuss the current prevalence of infection and future trends
- List animal models of infection
- Outline the current status of vaccine development

INTRODUCTION AND HISTORICAL BACKGROUND

Infection with Helicobacter pylori is one of the most common bacterial infections of humans. The infection is generally acquired early in life and has a particularly high incidence in countries with poor hygiene conditions. The bacterium colonizes the gastric mucosa leading to a life-long infection. A minority of infected individuals develop serious gastrointestinal diseases: chronic gastritis, gastroduodenal ulcers, adenocarcinoma, and lymphoma.

Extensive seroepidemiologic studies have shown an increased risk of gastric cancer in persons infected with H. pylori. Based on such studies the International Agency for Research on Cancer classified H. pylori as a type I carcinogen in 1994 (1).

The association of H. pylori with the development of gastric and duodenal ulcers has had a profound impact on the diagnosis and treatment of upper gastroduodenal diseases; gastric ulcer is now regarded an infectious disease that can be controlled with antibiotic treatment.

Early studies:

The presence of spiral-shaped bacteria in gastric washings and in the lining of human stomachs was first observed in the late 19th century. These bacteria were re-discovered in the early 1980s when Robin Warren and Barry Marshall were able to culture the unknown bacteria from stomach biopsy specimens taken from ulcer patients. In order to demonstrate the role of these bacteria in gastric disease Barry Marshall infected himself by drinking some of the bacterial culture. Symptoms of gastritis developed and spiral-shaped bacteria were recovered from his stomach lining, satisfying some of the four Koch’s postulates.

Marshall and Warren’s discovery that a bacterium was responsible for most cases of gastric disease was recognized in 2005 when they were awarded the Nobel Prize in physiology or medicine.

The spiral-shaped bacteria were originally named Campylobacter pyloridis (later changed of C. pylori). Subsequent studies involving partial sequencing of bacterial 16S RNA yielded evidence that the isolate belonged to a genus separate from Campylobacter. This was confirmed by nucleic acid hybridization profiles, growth characteristics, fatty acid profiles, and enzymatic activities of the isolate. The genus Helicobacter was established in 1989 and C. pylori was renamed Helicobacter pylori. In 1994 the Helicobacter pylori genome was sequenced. This
information made possible genotypic analysis of isolates from infected family members, thus greatly facilitating epidemiologic studies of *H. pylori* infection.

**GENUS HELICOBACTER: PRINCIPAL FEATURES**

The helicobacters are Gram negative bacteria that colonize the mammalian gastrointestinal tract. Close to two dozen species are included in the genus; of these, *H. pylori*, *H. cinaedi*, and *H. fennelliae* are human pathogens. The habitat of these organisms is, most probably, the human gastrointestinal tract. *H. cinaedi* and *H. fennelliae* may cause proctitis, enteritis, septicemia, and occasionally, cellulitis and meningitis in immunocompromised patients.

*H. pylori* occurs worldwide; infection is usually acquired in early childhood. It is estimated that by adulthood over half the world population is infected. Although primarily a human pathogen, *H. pylori* has been found to colonize some non-human primates. For example, captive rhesus monkeys are commonly infected. This infection is almost universal in adult animals and appears to be acquired at a very early age. The consequence of *H. pylori* infection is a chronic gastritis, similar to that observed in human patients. A few animals develop atrophic gastritis, a histologic precursor to gastric adenocarcinoma. The monkeys develop specific cellular immunity and circulating antibody. This immune response, however, is not sufficient to clear the infection. This resembles the course of *H. pylori* infection observed in humans (2).

The primary habitat of *H. pylori* is human gastric mucosa where it penetrates the mucous layer and attaches to the epithelial cells but does not invade the epithelium. The bacterium is well-adapted to its ecologic niche. It possesses attributes that permit its entry into the mucous layer, attachment to epithelial cells, neutralization of the acid pH of the stomach, and evasion of the immune response.

Morphologically *H. pylori* has many characteristics in common with campylobacters; both genera are Gram negative, have a spiral or helical shape, and are motile by a tuft of polar flagella (3). There is considerable genetic variability among *H. pylori* strains with marked variation in virulence.

*H. pylori* grows best at neutral pH; it is microaerophilic and will grow in the presence of 5% carbon dioxide. Enriched medium supplemented with antibiotics is used, such as Brucella agar with 5% calf serum and the antibiotics trimethoprim, vancomycin, and polymyxin. Other suitable media include Skirrow’s medium with antibiotics (as in Brucella agar), or chocolate agar with vancomycin, nalidixic acid, and amphotericin. Pinhead-sized, translucent colonies appear in 3 to 7 days. Microscopy and biochemical tests demonstrate curved Gram negative organisms that are oxidase positive, catalase positive, and urease positive. The urease reaction is strong and rapid; this reaction is one of the main identifying features of *H. pylori*.

**H. PYLORI AND HUMAN DISEASE**

Identification of clinical consequences of *H. pylori* infection is one of the major discoveries in gastroenterology within the last twenty-five years. Human gastric mucosa is the natural ecologic niche of *H. pylori*; however, unlike the commensal microorganisms that inhabit mucosal surfaces, *H. pylori* is capable of causing inflammation and disease at the site of infection. The inflammatory process does not lead to clearance of this infection. Possibly this pathogen has adapted to colonization of inflamed mucosal surfaces, making inflammation a prerequisite to prolonged colonization. The majority of infected individuals do not suffer from
associated gastrointestinal disease, but a proportion of infected persons develop acute gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma (MALT), or gastric adenocarcinoma.
Pathogenesis of *H. pylori* infection: colonization of gastric mucosa

*H. pylori*, assisted by polar flagella, colonizes the mucous layer that lies over the gastric epithelium, penetrates the mucous layer, but does not invade the epithelium. The bacterium persists in the gastric mucosa and causes tissue damage. Its location within the mucous layer helps it escape the acid environment of the stomach. *H. pylori* has acid-responsive genes expressed under acidic conditions: at pH5.5 the transcriptional activity of ammonia-producing enzymes is increased from four to nine-fold. Urease, in particular, is produced in abundance and creates a more alkaline microenvironment.

*H. pylori* adhesins (bacterial outer membrane proteins) enable the pathogen to bind to fucose-containing H and Lewis blood group antigens found in the gastrointestinal mucosa. It is noteworthy that blood type O persons are at a higher risk for ulcer disease than persons whose blood types are A, B, or AB.

*H. pylori* adherence to stomach mucosa attracts inflammatory and lymphoid cells. Presence of lymphoid cells in gastric mucosa is evidence of persistent inflammation, which can eventually lead to the destruction of normal epithelium, the loss of the mucous layer, and an increased cell turnover. This condition is called atrophic gastritis and is a serious risk for stomach cancer.

**Consequences of *H. pylori* infection**

The ability of the gastric mucosa to secrete acid affects the outcome of *H. pylori* infection. A higher acid output is likely to lead to ulceration; with a lower output, either gastric cancer or gastric ulcer may develop. Cytokines produced during inflammation may affect acid production; for example, interleukin 1-beta is acid-suppressive. This cytokine is commonly produced during a microbial infection and may play a role in the outcome of *H. pylori* infections in developing countries.

Dendritic cells may be affected in chronic infections. After prolonged exposure to bacterial antigens dendritic cells may show impaired cytokine production that affects T cell development.

Clinical consequences of *H. pylori* infection include gastritis, ulcers, and gastric malignancies.

**Gastritis**

In children, *H. pylori* gastritis appears to be asymptomatic. Adult patients may have acute dyspeptic symptoms, including pain, nausea, and indigestion. The symptoms usually last several days to two weeks. Eradication of the pathogen reduces symptoms in some but not in all patients, suggesting that factors other than *H. pylori* infection may cause dyspeptic symptoms in a general patient population. Chronic gastritis may lead to ulcers or gastric malignancies in susceptible hosts.

**Ulcers**

Approximately 10% of persons infected with *H. pylori* develop gastric or duodenal ulcers. The incidence of ulcers varies with geographic region and ranges from 3% to 25%. An on-going *H. pylori* infection is a major factor in ulcer disease.

**Gastric malignancy**

A. Gastric lymphoma

*H. pylori*-related low-grade gastric MALT lymphoma represents the first described neoplasm susceptible to regression following antibiotic therapy. Tumor cells of MALT lymphoma are memory B cells that respond to differentiation signals and to
cytokines produced by antigen-stimulated T-helper cells. These B cells are dependent on stimulation by \( H. pylori \)-specific T cells for their growth. Eradication of \( H. pylori \) infection is a major factor in regression of MALT lymphoma.

B. Gastric adenocarcinoma

This is one of the leading causes of cancer-related deaths in the world and is the fifth or sixth most common cause of newly diagnosed cancer in some European countries. The risk of developing gastric adenocarcinoma is increased by a factor of two in persons infected with \( H. pylori \). The genotype of the infecting strain is important, as well as a number of host factors. For instance, strains with the cytotoxin-associated gene (CAGA gene) are implicated more frequently in gastric cancer. Among host-related factors the acquisition of infection at a very early age, a positive family history of gastric cancer, and bacterial–host genotype interaction appear important in cancer development.

Other conditions associated with \( H. pylori \) infection

A. Gastric atrophy

This condition shows a relationship to autoimmune chronic gastritis. The latter is an organ specific inflammatory disease leading to gastric atrophy and pernicious anemia. \( H. pylori \) infection can activate some of the gastric T cells leading to gastric autoimmunity in genetically susceptible persons.

B. Miscellaneous clinical conditions

\( H. pylori \) infection may be associated with the following conditions:
- Gastroesophageal reflux disease
- Iron deficiency anemia
- Rheumatologic conditions
- Inflammation of the coronary arteries
- Certain skin conditions

Beneficial effects of \( H. pylori \) infection

Infection with \( H. pylori \) may protect the host from other gastrointestinal bacterial infections because of antibacterial peptides produced by \( H. pylori \).

Possible effect on esophageal cancer: \( H. pylori \) strains that release cytotoxin-associated antigen (Cag A) are able to destroy esophageal cancer cells grown \textit{in vitro}.

VIRULENCE FACTORS, HOST RESPONSE, AND METHODS OF DIAGNOSIS

Virulence Factors

A. Helicoidal shape and flagella of \( H. pylori \): these characteristics assist the bacterium in reaching the gastric mucosa. \( H. pylori \) must cross the oral cavity and the esophageal tract, enter the acidic environment of the stomach and penetrate the mucus layer that covers the gastric mucosa.

B. Catalase: this enzyme helps \( H. pylori \) survive in the host by preventing the formation of reactive oxygen metabolites from hydrogen peroxide.

C. Adhesins: these are immunogenic membrane proteins expressed in a subgroup of \( H. pylori \) strains. Adhesins allow the bacterium to bind to receptors on the surface of gastric epithelial cells. The process of binding causes reorganization of the plasma membrane of the cells, providing access to nutrients within the damaged gastric epithelium. Adherence to gastric epithelium also stabilizes the bacterium against mucosal shedding into the
gastric lumen. Bacterial strains expressing adhesins are associated with intestinal metaplasia and atrophic gastritis.

D. Lipopolysaccharide (LPS) in bacterial outer membrane: LPS mediates outer membrane permeability; it may induce autoantibodies to gastric cells, facilitating development of gastric atrophy. LPS has certain antigenic groupings that resemble the Lewis blood group antigens, some of which may function as adhesins.

E. Enzymes involved in nitrogen metabolism: the activity of these enzymes generates ammonia, which is important to *H. pylori* as a nitrogen source, as protection against gastric acidity, and as a cytotoxic molecule that produces tissue damage during colonization. The ammonia-producing enzymes of *H. pylori* include urease, deaminases, deamidases, and two aliphatic amidases that hydrolyze short-chain amides to produce ammonia and the corresponding organic acid. Urease is the most abundant of these enzymes, constituting from 5% to 10% of total protein content. Urease is essential for *H. pylori* in colonization of gastric mucosa; it neutralizes gastric acidity and it induces activation and adherence of inflammatory cells in the area of colonization.

F. Mucus-hydrolyzing enzymes: these enzymes aid the bacterium in entering the mucus layer of the gastric mucosa.

G. Vacuolating cytotoxin (Vac A), coded by the VACA gene: this important virulence factor is formed by approximately 40% of *H. pylori* strains. This exotoxin causes progressive vacuolation of cells and gastric injury. Vac A induces multiple effects on epithelial and lymphatic cells. These effects include the following: inducing inflammatory cytokines and increasing the inflammatory response; inhibiting T cell activity; causing intracellular damage that may interfere with antigen processing. After the cytotoxin binds to the plasma membrane of a target cell it is internalized. Within cells the toxin induces:

1. rearrangement in the organization of endosomes and lysosomes
2. extensive membrane fusion and swelling
3. vacuole formation
   - The vacuole facilitates intracellular survival of *H. pylori*: the vacoule protecting the pathogen from inflammatory cells and limiting access of antibiotics.

H. Cytotoxin-associated antigen (Cag A): this is a major virulence factor of *H. pylori*, coded by the Cag A gene and found in approximately 60% of *H. pylori* strains. Infection with strains of *H. pylori* that synthesize Cag A is linked to peptic ulcer disease and gastric carcinoma. Cag A is coded by a gene that is located within the so-called cag pathogenicity island (a cluster of genes coding cytotoxins and associated proteins). Some of these proteins assemble into a molecular syringe and translocate Cag A into gastric epithelial cells. This disrupts the function of the epithelial barrier, damages intercellular junctions and causes an alteration in epithelial cell morphology. (4)

I. Neutrophil-activating protein (NAP): this virulence factor has a number of functions:
   1. acts as an adhesin, mediating binding to mucus
   2. is chemotactic for neutrophils and monocytes
   3. promotes neutrophil adhesion to endothelial cells
   4. induces neutrophils to produce reactive oxygen radicals
   5. can activate mast cells with release of proinflammatory cytokines
6. plays a role in iron uptake by *H. pylori* (iron is an essential nutrient for this bacterium).
7. Host Response to Infection

Non specific defense mechanisms

Host response to *H. pylori* infection is characterized by a strong inflammatory reaction and production of various cytokines. Interleukin-8 (IL-8) expressed by gastric epithelial cells is chemotactic for neutrophils, thus contributing to the inflammatory cascade. Activation of macrophages results in the release of IL-12, IL-1, IL-6, and IL-8, as well as tumor necrosis factor-alpha and interferon-alpha. These cytokines, particularly IL-12, direct the subsequent T cell response toward a pattern where T helper (Th) cells of the Th1 subset predominate.

*H. pylori* is able to survive within activated macrophages by interfering with lysosomal proteins. In general, the inflammatory response is not sufficiently effective to eliminate the infection.

Specific immune response

*H. pylori* infection stimulates a specific response which includes circulating antibody and secretory immunoglobulin A. In addition to antibody, activated mucosal and circulating T cells can be demonstrated; these tend to be Th 1 cells. Studies of activated T cells indicate that Th 2 cells rather than Th 1 mediate protective immunity. The vigorous immune response of the infected host does not eliminate *H. pylori* infection.

Methods of Diagnosis

Diagnostic tests for *H. pylori* infection fall into two categories: invasive and non-invasive.

A. Non-invasive tests:

- Serology: a number of enzyme immunoassay tests are available. These detect both past and current infection.

  In epidemiologic studies, the immunoblot assay with anti-Cag A antibody has been used successfully.

- Urea breath test: the patient ingests radioactively-labeled urea; if *H. pylori* infection is present, urease produced by the bacterium will hydrolyze urea to ammonia and bicarbonate. The labeled carbon dioxide is exhaled and can be detected with a spectrometer or a scintillation counter. The urea breath test is the preferable non-invasive diagnostic procedure. It detects only current infection.

Fecal Antigen tests. Several procedures are available:

1. Polymerase chain reaction (PCR) for direct detection of the bacterial DNA in stool specimens; detection rates vary from 25% to 100%
2. Purification of bacterial DNA from stool using a gene capture method followed by PCR
3. Detection of bacterial antigen in feces using enzyme immunoassays
4. Fecal antigen test kits are available, such as Amplified-IDEA-HpStAR (Denmark), which utilizes monoclonal antibody and has excellent reproducibility. An office-based antigen test, ImmunoCard STAT HpSA (Meridian) also uses monoclonal antibody.

B. Invasive tests: endoscopy and collection of a gastric biopsy specimen. Diagnosis of *H. pylori* infection may be accomplished by histologic examination, rapid urease testing, PCR, or culture of biopsy specimen.
1. Histology: biopsy specimens can be stained with Giemsa or silver stains and examined directly for typical organisms. Squash preparations of biopsy material can be Gram-stained using 0.1% basic fuchsin as counterstain.

2. Urease test: a portion of crushed tissue biopsy is placed directly into urea broth or into commercially available urease agar kits. A positive test is considered indicative of *H. pylori* infection.

3. Cultures: biopsies are placed in vials with Brucella broth for transport to the laboratory. Tissue is homogenized and plated on enriched medium supplemented with antibiotics and incubated at 37°C in 5% carbon dioxide atmosphere.

4. PCR assay of gastric biopsy specimens can be used in place of culture; this procedure has 97% sensitivity and 94.6% specificity.

EPIDEMIOLOGY OF *H. PYLORI* INFECTION

It is estimated that close to half of the world’s population is infected with *H. pylori*; there is, however, a distinct difference in the prevalence of this infection between developed and underdeveloped countries. Humans are the identified source of infection; contact with animals is not associated with an increased risk of acquiring infection. (5)

**Transmission:**

Children acquire the infection as infants. Epidemiologic studies show that transmission occurs within families. The mother may play a major role in transmitting the infection to the child; transmission between siblings of similar age may also occur. DNA typing has shown that the same bacterial strain is generally found among family members.

The bacteria have been isolated from feces, saliva, and dental plaque of infected patients, suggesting possible fecal-oral and oral-oral transmission routes.

Most infections are acquired between the ages of 2 to 5 years. Although infection with *H. pylori* is considered chronic and not self-limiting, there are some indications that elimination of the pathogen may occur. In developed countries re-infection is infrequent.

**Prevalence of infection:**

The prevalence of infection in both children and adults shows strong regional differences. Depending on the child’s age, prevalence varies from 0% to approximately 30%. Prevalence in adults increases with age and varies among study populations. Among adults aged 56 to 66 years prevalence may reach 82%. In addition to age, the person’s race affects susceptibility to clinical disease; approximately 29% of cases are among whites, with 60% of cases among Hispanics. Since this infection is acquired during childhood, an increase in the prevalence of infection with age reflects childhood living conditions. The infection rate in children has been showing a steady decline in developed countries, possibly as a result of improved sanitation and better hygiene practices and living conditions. This trend has important implications for associated diseases in adulthood.

*H. pylori* infection and gastric malignancy:

In developed countries a decrease in incidence of gastric cancer has been recorded within the past few decades. On a world-wide scale (both developed and underdeveloped countries), however, the rate is increasing due to an increasing life span. There is considerable geographic variation in the number of new cancer cases. More than half of newly diagnosed gastric cancer cases are in Eastern Asia. Based on gastric cancer incidence rates, Japan, Korea, and China are considered high risk areas. An interesting phenomenon is the “Asian Paradox”: *H. pylori* infection rate is high in areas with low incidence of gastric cancer, such as South-Central and
South-Eastern Asia, while infection incidence is lower in Eastern Asia where the cancer incidence is the highest in the world.

Despite a clear-cut association between *H. pylori* infection and gastric cancer, other factors appear to be involved: smoking, the strain of *H. pylori*, the presence of certain virulence factors, host genetic make-up, and the host’s response to chronic infection.

EXPERIMENTAL MODELS OF INFECTION

Experimental animal models have included a wide range of species, including pigs, non-human primates, cats, dogs, and rodents (mice in particular). The first animal model for *Helicobacter* infection was developed in mice with a mouse-adapted *H. pylori* strain. These studies provided information on bacterial and host factors involved in disease pathogenesis.

Important bacterial factors:

1. Motility
2. Urease activity
3. Effective iron uptake and iron storage mechanisms
4. Presence of protective enzymes such as superoxide dismutase and oxidase

By contrast, bacterial virulence factors, such as cag A or vac A were not essential for bacterial colonization.

Important host factors:

1. Genetic make-up of the host
2. Induction of cytokines, such as IL-17, which promote inflammation
3. Nature of the normal microbial flora of the gut
4. Host immune response, including T helper cell phenotype and specific cytokines produced by Th 1 or Th 2 cells.

Examples of experimental animal models:

A. Model of *H. pylori* gastritis in experimental rats
   A gastritis model has been recently developed in Wistar rats. Gastritis was induced in rats using a *H. pylori* strain isolated from a biopsy taken from a male patient. The rats sustained pronounced injury in mucosal tissue and suffered massive oxidative stress. These symptoms reflect the clinical picture of *H. pylori* infection.

B. Gastric adenocarcinoma in Mongolian gerbils
   Long-term infection of Mongolian gerbils provided first experimental evidence that *Helicobacter* infection can result in the development of gastric adenocarcinoma. The pathology is similar to that in humans. Key factors in the neoplastic process include elevated levels of serum gastrin, decreased gastric acid production, and elevated levels of IL–1 beta and of the regulators of the cell cycle progression.

C. MALT lymphoma in ferrets and mice
   Gastric B cell mucosa-associated lymphoid tissue (MALT) lymphoma was developed in ferrets and in mice. Treatment and eradication of *Helicobacter* infection resulted in tumour regression in a high percentage of test animals.

TREATMENT AND VACCINE DEVELOPMENT

Peptic ulcer disease is now approached as an infectious disease and effective treatment is available. A number of antimicrobial compounds are active against *H. pylori*. Because of gastric acidity, which affects some antimicrobial agents, an antisecretory compound is usually included with the antibiotics. A combination of two or more antimicrobial agents increases rates
of cure and reduces the risk of selecting for resistant mutant strains. Such “triple therapies” (combinations of an antisecretory agent with two antimicrobial compounds) are generally administered for one to two weeks. A number of such therapies have been evaluated and several treatment regimens have been approved by the Food and Drug Administration. Several antisecretory compounds are available for clinical use: omeprazole, pantoprazole, and related compounds. These drugs are so-called “proton pump” inhibitors; their main action is interference with the terminal stage in gastric acid secretion.

**Antimicrobial agents**

The chief antimicrobial agents used are amoxicillin, clarithromycin, metronidazole, tetracycline, and bismuth. The frequency of clarithromycin resistance is around 10%; resistance to metronidazole ranges between 20% and 30%. Successful treatment produces cure rates of 80% or higher. In cases where primary treatment has failed, either because of poor patient compliance or antibiotic resistance, a second 10 to 14 day treatment course is recommended. The choice of drugs for the second treatment should be guided by the results of susceptibility tests. If this information is not available, antibiotics used in primary therapy should be avoided.

**Guidelines for treatment of *H. pylori* infection**

Treatment is **recommended** for patients with the following conditions:

1. Duodenal or gastric ulcer
2. MALT lymphoma
3. Atrophic gastritis
4. Gastric cancer
5. First-degree relative of patient with gastric cancer
6. Patient requests treatment after medical consultation

Treatment is **advisory** for the following:

1. Dyspepsia
2. Gastrooesophageal reflux disease
3. Patient taking non-steroid anti-inflammatory compounds (NSAIDs), since these compounds are an independent risk factor for peptic ulcer disease

**Antibiotic therapy**, although effective, has not eliminated *H. pylori* infection for following reasons:

1. Re-infection or failure of treatment
2. Infected persons who do not show clinical symptom and are not treated
3. Cost of treatment

**Vaccine Development**

Vaccines represent one of the most effective approaches for control of infectious disease. The development of a vaccine requires a suitable antigen, a strong and effective adjuvant, and an optimal route of inoculation. Antigens tested in *H. pylori* vaccine studies have included inactivated whole-cell preparations, urease enzyme, and other bacterial virulence factors. Purified recombinant proteins proved poorly immunogenic and required strong mucosal adjuvants.

**Vaccine tests: animal studies**

Several animal models have been used: mice, monkeys, and dogs. Prophylactic protection as well as therapeutic effectiveness was demonstrated in mice and in monkeys, using *H. pylori* urease or virulence proteins with *E. coli* heat-labile enterotoxin as adjuvant.

**Vaccine tests: human studies**
A recombinant protein vaccine has been developed by Chiron Corporation (now Novartis Vaccines). This vaccine consists of three \textit{H. pylori} proteins, Vac A, Cag A, and neutrophil-activating protein (NAP), with aluminum hydroxide as adjuvant. The vaccine is undergoing clinical trials.

SUMMARY

\textit{Helicobacter pylori} is one of the most common bacterial pathogens; it infects the gastric mucosa in humans and is found world-wide.

When first observed in gastric biopsies and cultivated in the laboratory, this bacterium was classified as \textit{Campylobacter pylori}. Subsequent studies led to establishment of a new genus \textit{Helicobacter} and the re-classification of this pathogen as \textit{Helicobacter pylori}. This bacterium is Gram negative, spiral-shaped, and motile by polar flagella. It can be cultured on enriched medium in the presence of 5% carbon dioxide. Its most notable biochemical activity is the production of large quantities of urease.

Infection with \textit{H. pylori} is world-wide; the incidence is high but varies with the geographic area. The majority of infected persons have no symptoms of disease; however, a certain proportion of infected population will develop acute gastritis or gastric or duodenal ulcers. Some persons may develop gastric cancers. Because of strong association between gastric cancer and \textit{H. pylori} infection this bacterium is classified as a bacterial carcinogen. The strong immune response of the infected host does not eliminate the infection.

\textit{H. pylori} possesses a number of virulence factors that facilitate colonization of gastric mucosa. The infection can be diagnosed by the urea breath test, serology, stool antigen tests, or gastric biopsy accompanied by culture or PCR.

Experimental models of infection have yielded valuable information on factors required for colonization of gastric mucosa. Models of gastric cancer had been developed in several animal species.

Effective antibiotic treatment is available for \textit{H. pylori} infection; a combination of two antimicrobial compounds with an antisecretory agent is used; several treatment regimens have been approved by the Food and Drug Administration.
REFERENCES

REVIEW QUESTIONS
DL-957

Select the **one** best answer

1. A distinguishing feature of *H. pylori* is:
   a. it is not immunogenic
   b. it is highly invasive
   c. it produces the enzyme urease
   d. it does not produce any toxins

2. *H. pylori* infections are:
   a. likely to occur mostly in old age
   b. acute rather than chronic
   c. associated with two types of gastric cancer
   d. very rare events

3. The majority of persons infected with *H. pylori*:
   a. have severe diarrhea symptoms
   b. develop antibody to *H. pylori*
   c. develop ulcers
   d. develop gastric cancer

4. Antibiotic treatment of a patient with *H. pylori* infection and MALT lymphoma may result in:
   a. regression of MALT lymphoma
   b. spread of infection beyond the intestinal tract
   c. progression of the lymphoma
   d. development of ulcers

5. Which of the following proteins synthesized by *H. pylori* is **not** a virulence factor?
   a. urease
   b. oxidase
   c. neutrophil-activating protein
   d. Cag A protein

6. Survival of *H. pylori* within infected cells is aided by:
   a. activity of oxidase enzyme
   b. vacuolating toxin
   c. Cag pathogenicity island
   d. cytotoxin-associated antigen
7. Which of the following is not one of Cag A attributes:
   a. disrupts host cell intercellular junctions
   b. is linked to development of ulcers and gastric cancer
   c. facilitates iron uptake by \textit{H. pylori}
   d. is coded by genes in Cag pathogenicity island

8. Infection with \textit{H. pylori} is characterized by:
   a. lack of inflammatory response
   b. absence of specific circulating antibody
   c. absence of cytokine response
   d. activated mucosal and circulating T cells

9. Eradication of \textit{H. pylori} infection may be achieved by:
   a. the inflammatory response of the host
   b. the activity of interleukins
   c. the activity of mucosal T cells
   d. antibiotic therapy in addition to the immune response

10. A common method used in diagnosis of \textit{H. pylori} infection is:
    a. stool culture
    b. blood culture
    c. urea breath test
    d. Gram stain of a throat swab

11. \textit{H. Pylori} has the following characteristics:
    a. it can not be observed in Gram-stained preparations
    b. it can be cultivated from gastric biopsies of infected persons
    c. can be easily grown from stool samples
    d. it will grow on plain agar anaerobically

12. Antimicrobial treatment of \textit{H. pylori} infection may include:
    a. streptomycin
    b. bismuth compounds
    c. sulfa drugs
    d. bacitracin

13. The duration of \textit{H. pylori} infection treatment regimen is:
    a. a single dose of the antibiotics
    b. a 72-hour treatment regimen
    c. a one- to two-week treatment regimen
    d. treatment must continue indefinitely
14. Triple drug therapy for ulcers would consist of:
   a. milk, a sedative, and an antibiotic
   b. aspirin and two antibiotics
   c. an antisecretory compound and two antibiotics
   d. an antisecretory compound and aspirin

15. Transmission of *H. pylori* infection involves:
   a. an arthropod vector
   b. an animal reservoir of infection
   c. familial spread from mother to child
   d. the respiratory route

16. The incidence of *H. pylori* infection in young children is:
   a. decreasing in developed countries
   b. increasing in developed countries
   c. shows no change in developed countries
   d. decreasing in underdeveloped countries

17. In developed countries *H. pylori* infection in adults is expected to show:
   a. an increase in infection rate in the future
   b. a decline in infection rate
   c. an increase in severity of symptoms
   d. the infection rate will remain stable

18. Natural *Helicobacter* infections occur:
   a. only in humans
   b. in humans and in some non-human primates
   c. mostly in cats
   d. in most rodent species

19. Development of MALT lymphoma in experimental animals was shown in:
   a. rabbits
   b. monkeys
   c. Mongolian gerbils
   d. mice

20. A *Helicobacter pylori* vaccine:
   a. uses a living bacterial antigen
   b. is ready for use in humans
   c. has shown some success in animal tests
   d. has not been tested in humans