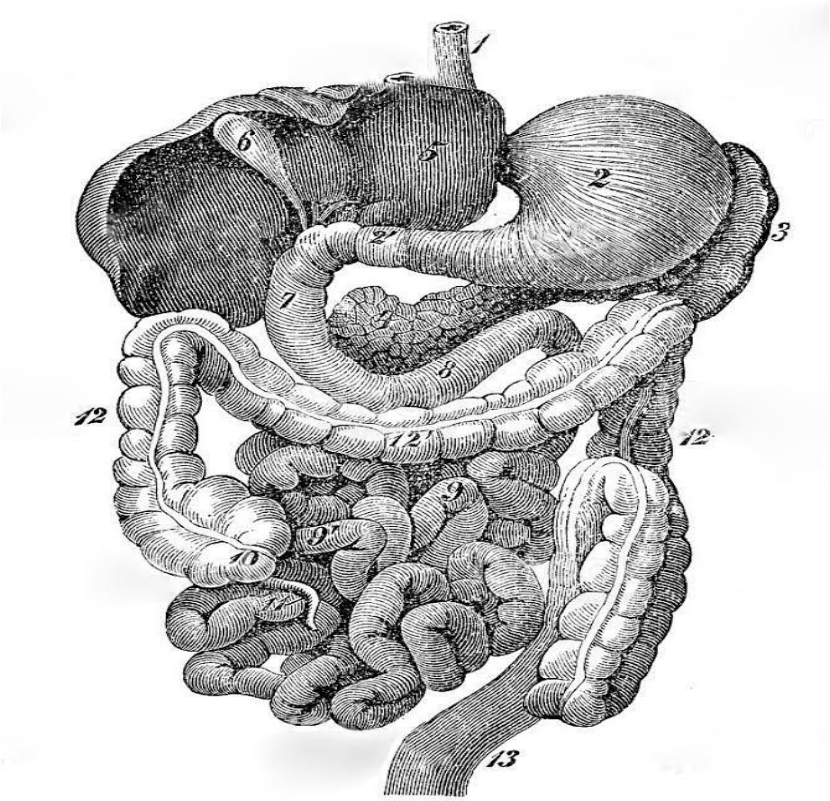
# Microbiology

## 435's Teamwork
## GastroIntestinal & Nutrition Block




- Kindly check our Editing File before studying the document.
- Please contact the team leaders for any suggestion, question or correction.
- Pay attention to the statements highlighted in red.
- Extra explanations are added for your understanding in grey.
- **Footnotes color code:** General | Females | Males.
- **color code:** Female's notes | Male's notes.

# Role of *H.pylori* in Peptic Ulcer and drugs used in Treatment

**Resources:** Sherris Medical Microbiology, Doctor's slides+notes 2016,...

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## Learning Objectives: (from us)

**By the end of this lecture, you should know the…**

- Peptic ulcer disease
- Epidemiology, Description, Laboratory characteristics, diagnosis and treatment..

**Of Helicobacter pylori.**

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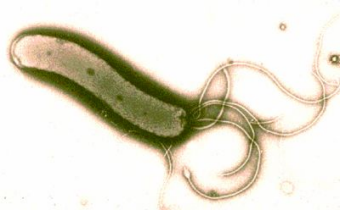
## Peptic Ulcer Disease (PUD)- القرحة الهضمية

-We recommend to study this point from pathology's lecture first

| Definition | Location | Complication | Signs & Symptoms |
|---|---|---|---|
| Is an ulcer defined as mucosal erosions (≥ 0.5cm) associated with the over usage of NSAIDs. | •Peptic ulcer is created in an **acidic area** (very painful).<br>•More Peptic ulcers are arise in **duodenum** than stomach.؟ليش<br>لأن الاسيدتي أقل في duodenum | •4% of stomach ulcer can turn to be **malignant tumor.**<br>•Duodenal ulcers are generally **benign**.<br>(Multiple biopsies are needed to exclude cancer) | •**Abdominal pain**, epigastric with severity relating to meal time (3 hours after meal with gastric ulcer).<br>Before the meal may indicates duodenum ulcer.<br>- Bloating and abdominal fullness.<br>- **Nausea** and **vomiting**.<br>- Loss of appetite and **weight loss**.<br>- **Haematemesis** (vomiting of blood) due to gastric or esophagus damage.<br>- Melena (foul-smelling & dark brown faeces due to oxidized hemoglobin iron).<br>- Rarely, Gastric or duodenal perforation leading to acute peritonitis(extremely painful-require urgent surgery.من أسوء المضاعفات تخترق جدار المعدة او الامعاء. |

# *Helicobacter pylori*

-highly recommended Video

| Description | | | |
|---|---|---|---|
| **Fastidious in terms of growth requirements**[1] | | | **Morphology** |
| اهم شيء تعرف انها **Strictly Microaerophilic** تحتاج كمية قليلة من الاكسجين لكي تنمو ولكن الكمية الكبيرة من الاوكسجين كالهواء الطبيعي يقتلها لذلك نستخدم الـ CO 2 | Require C02 for growth/ charcoal[2]  | On chocolate agar medium  | Small, Gram-negative, Spiral rods(Bacilli), Motile by polar **flagella**.  |

## Pathophysiology

1)H. pylori is unusual in its ability to colonize the stomach, where low pH normally protects against bacterial infection; To **colonize** the stomach, *H pylori* must survive acidity. أول خطوة لإحداث المرض هي الاستعمار

2)Using **flagella**, *H pylori* moves through stomach lumen and **drill** into the mucoid lining of stomach→Produces adhesions that **binds** to the epithelial cells.

3)Produces large amounts of **urease**[3] enzyme that break down urea into co2 +ammonia→This in-turn neutralizes[4] gastric acid favoring bacterial multiplication→Ammonia is toxic to epithelial cells along with **proteases, vacA** protein and phospholipases produced by *H pylori* and could damage epithelial cells.

البكتيريا تموت من الحموضة حقت المعدة لذلك تفرز اليورياز الذي يكسر اليوريا ويعطينا الأمونيا التي تعتبر قاعدة لتعادل الحموضة حقت المعدة حول البكتيريا.

4)The organism is noninvasive, but recruits and activates inflammatory cells, thus causing a chronic inflammation of the mucosa Colonization of **stomach** or **duodenum** results in chronic gastritis (inflammation of stomach lining)→Inflammation stimulate more production of gastric acid→This leads to **gastric** and **duodenal ulcers**, **atrophy** and **later cancer**.الطفرات تحدث قبل أن يحدث السرطان

- CagA protein was found to contribute to peptic ulcer.
- **Neutrophil-Activating Protein (NAP)** recruits neutrophils to gastric mucosa causing inflammation.
- **Free radical** production in the gastric lining due to *H pylori* , increases host cell mutation.
- *H pylori* induces the production of TNF-α and Interleukin 8 that leads to host cells **mutation**.

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[1] شديدة الحساسية تحتاج متطلبات لكي تنمو

[2] يستخدم الفحم آجار لزراعة الميكروبات الحساسية

[3] Without Urease can't survive in acidic stomach (أقوى و أهم شيء تطلعه هالبكتريا)

[4] Neutralize area around it not all stomach

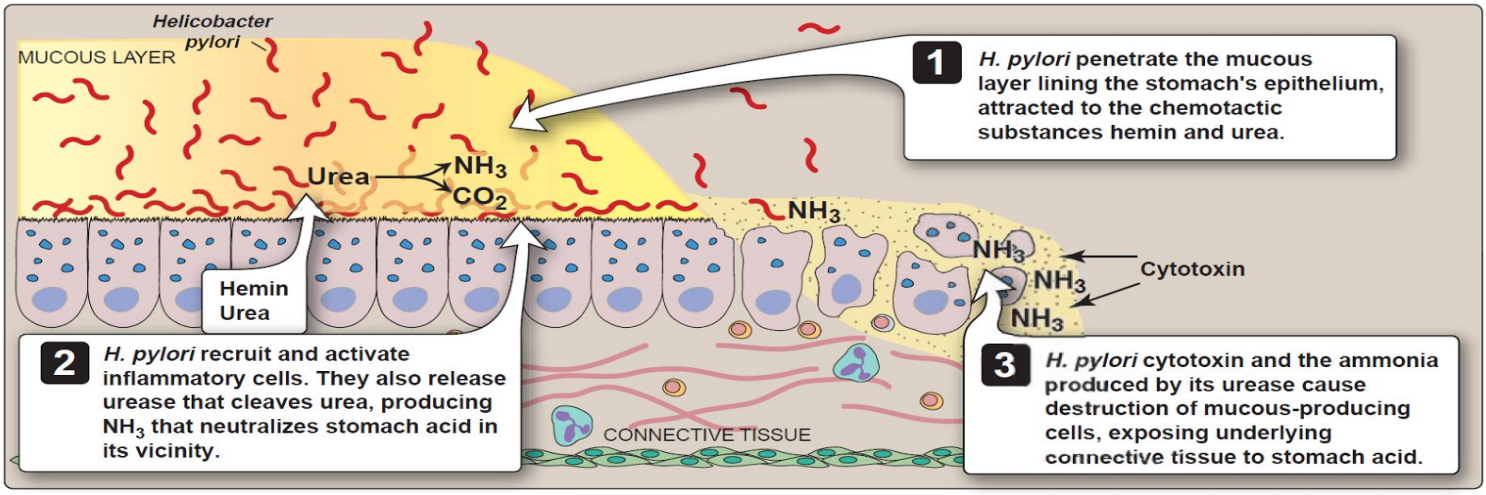
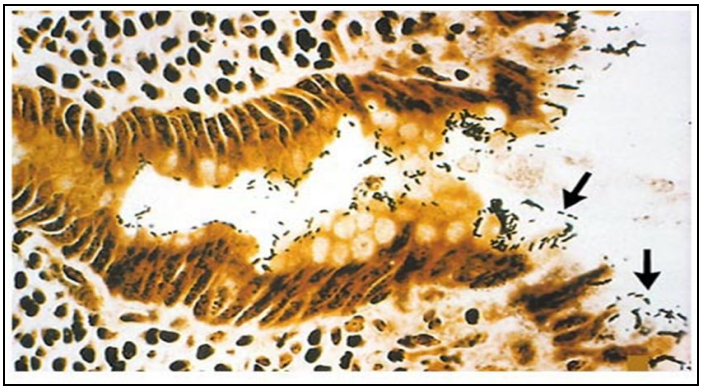
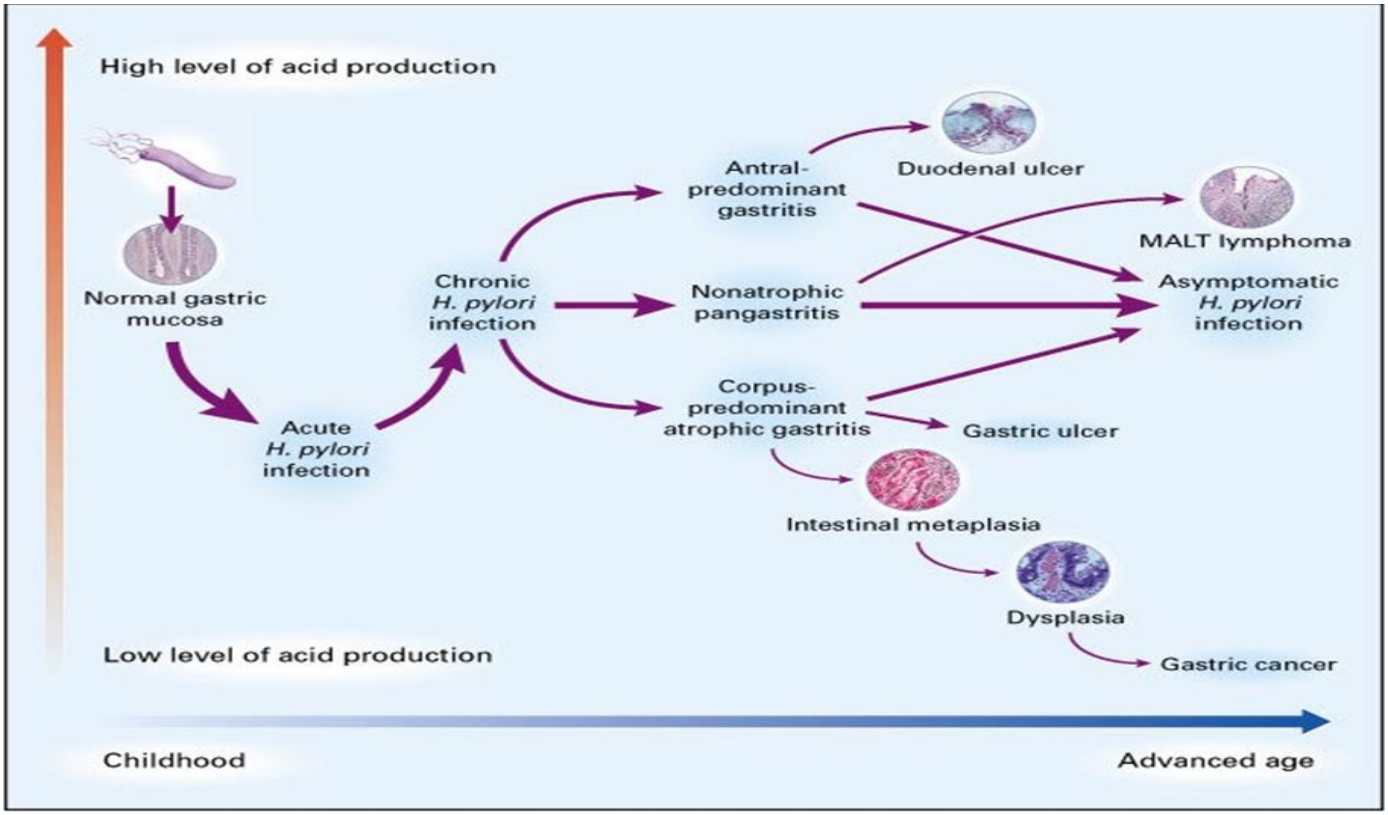



**Figure 12.17**
*Helicobacter pylori* infection, resulting in ulceration of the stomach.



- Gastric-biopsy specimen showing *Helicobacter pylori* adhering to gastric epithelium and underlying inflammation



| Transmission | Epidemiology | Prevention |
|---|---|---|
| •Contagious[5] with an unknown route of transmission .<br>•**Person to person** (**oral to oral or fecal-oral)** route.<br>•Transmission occur mainly within families or community.<br>•Fecal-oral route of infection occur by ingestion contaminated food or water due poor hygiene.<br>•Using same spoons, forks and tooth brushes and kissing children mouth to mouth increases oral-oral route of infection.<br>•**Gastric antrum** is the most favoured site.<br>•Present in the mucus that overlies the mucosa. | •More than 50% of the world's population harbour *H. pylori*[6] in their upper gastrointestinal tract.<br>- Third world has more rate of infection.<br>- Infections are usually acquired at childhood.<br>- Poor sanitary[7] conditions contribute to high rates.<br>- In USA high prevalence among African-American and Hispanic population-Due to socioeconomic status.<br>- Higher hygiene standards and widespread use of antibiotics behind lower rate of infection in the west.<br>- Overall frequency of *H pylori* infection is **declining**.<br>- Prevalence varies greatly among countries and population groups.<br>- Over 80% of individuals infected with the bacterium are **asymptomatic**[8]. | **-Eradication of infection will improve symptoms**:<br>Such as (dyspepsia, gastritis, peptic ulcer and cancer).<br>**-Vaccination:**[9]antigens.Promising results with studying adjuvant,<br>Determining route of immunization (oral or intramuscular).[10]<br>**-Dietary methods:** (eating broccoli, cabbage, honey, and drinking green tea)<br>**-Proper sanitation and clean sources of drinking water.** |

[5] معدي

[6] The **cagA gene** codes for the major H pylori virulence proteins.

[7] Poor hygiene and health

[8] Asymptomatic patients carry H pylori strains lacking the Cag pathogenicity island (PAI)**.**

[9] يقولك أنه الحين مافي لقاح مستخدم لكن في دراسات واعده أنه بالمستقبل القريب بيطلع لقاحات قوية.

[10] Oral rout will induce intestinal IgA

| Clinical manifestations |
|---|
| - *Helicobacter pylori* is found closely associated with gastric mucosa and causes chronic active gastritis, gastric and duodenal ulcer (Peptic ulcer) and could develop adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.<br>- *H.pylori* plays a role in gastric and duodenal ulceration and probably also **gastric cancer.**<br>- Nearly 20 species of *Helicobacter* are now recognised.<br>- Asymptomatic patients carry H pylori strains **lacking** the **Cag pathogenicity island (PAI).** |

| Laboratory characteristics | |
|---|---|
| **Culture** | - On blood or chocolate agar in a moist microaerophilic atmosphere.<br>- For isolation from clinical specimens, use **campylobacter** selective medium. Small colonies grow after 5-7 days at 37˚C. very slow growing bacteria |
| **Biochemical reactions** | - **Catalase-positive**.<br>- **Oxidase-positive**.<br>- **Strongly urease-positive:** the most important finding,hallmark of the species is production of urease enzyme,Urease breaks urea down to →c02+nh3,ammonia is a strong base process helps h. Pylori survive strongly acidic stomach conditions |
| **Typing**[11][12] | - A variety of nucleic acid methods have been developed, but there is no agreed typing scheme. |
| **Serology** | - **IgG and IgM** to Cytotoxin Associated Gene A (CagA) and (VacA) for virulence strains |
| Very fragile (a point of importance when referring samples to the lab) | |

[11]The process of differentiating strains based on their phenotypic and genotypic differences is known as 'typing'
[12] Not important

<table>
<tr><th colspan="2">Diagnosis:Checking for dyspeptic patients for H pylori.</th></tr>
<tr><th>Non-invasive methods<br>First choice</th><th>Invasive methods (most reliable)</th></tr>
<tr><td>Serology[13] (Blood antibody)<br>- Tests (IgG, IgM or IgA), poor accuracy<br>مو دقيقة لانه ممكن تلقى الأجسام المضادة حتى بعد سنين من الشفاء</td><td>Histological examination of biopsy specimens of gastric/duodenal mucosa take at endoscopy.<br>Very reliable, The gold standard الطريقة المثلى للتشخيص</td></tr>
<tr><td rowspan="2">Stool antigen test very specific<br>(Reliable but may there cross react with other bacteria)</td><td>CLO-test [14]<br>based again on urease-production by the organism->NH3 production->rise in pH=>change in the colour indicator of the kit<br>-High sensitivity and specificity-Prompt result.<br>  <br></td></tr>
<tr><td>Carbon urea breath test (C<sup>14</sup> or C<sup>13</sup>).[15]<br>very specific but very expensive<br>a urea solution labelled with C14 isotope is given to pt. The C02 subsequently exhaled by the pt contains the C14 isotope and this is measured. A high reading indicates presence of H. Pylori.</td><td rowspan="2">Endoscopy followed by culturing the bacteria.<br>used for antibiotic resistance testing, as sensitive as the histology. Requires selective agars and incubation periods.</td></tr>
<tr><td>Polymerase chain reaction (PCR)</td></tr>
</table>

- **The outcome of infection by *H. pylori* reflects an interaction between:**

(Strain virulence - Environmental factors - Host genotype)

[13] Can't use in monitoring patient

[14] عبارة عن انبوب يحتوي على يوريا تجيب الخزعة وتحطها فيه اذا تغير لون المحلول فهذا يدل على وجود *h.pylori*

[15] Breath tests involve administering radioactively labeled urea by mouth. If H. pylori are present in the patient's stomach, the urease produced by the organism will split the urea to CO2 (radioactively labeled and exhaled) and NH3

- **Antibiotic sensitivity:**

- In vitro[16] *H.pylori* is **sensitive** to amoxicillin, tetracycline, metronidazole, macrolides (clarithromycin).
- However, in vivo[17] their efficacy is often poor due to the low pH of the stomach, their failure to **penetrate** the gastric mucus and the low concentration of antibiotic obtained in the mucosa of the stomach.
- Recently , Metronidazole in developing countries is becoming resistance (80-90%).[18]

| **Treatment[19] Very IMPORTANT** | |
|---|---|
| **Triple therapies (first line)** | |
| Combination | Duration |
| **Proton pump inhibitor** + **Clarithromycin** + **Amoxicillin** 1000mg b.d (o**r metronidazole**[20] 500md b.d ). | Minimum of 7 days |
| **Quadruple Therapies (second line)** | |
| Combination | Duration |
| **Proton pump inhibitor (PPI)** + **bismuth**[21] **subsalicylate/subcitrate** 120mg QDS (4 times a day) + **Metronidazole** 500mg t.d.s. (3 times a day) + **Tetracycline** 500mg q.d.s.[22]<br>● If bismuth is not available, ppi based triple therapies should be used[23] | Minimum of 7 days |
| Proton pump inhibitor **(Omeprazole)**+ **Ranitidine Bismuth Citrate** +**Amoxycillin**+**Metronidazole** | |

- **Quadruple therapies:**

- Have shown to increase the eradication rate up to 98%. Unfortunately it was followed by side effects such as vaginal candidiasis in 10% of women and pseudomembranous colitis [24] in 11% of patient.
- Subsequent failures should be handled on a case-case basis. Patients failing second-line therapy in primary care should be referred.

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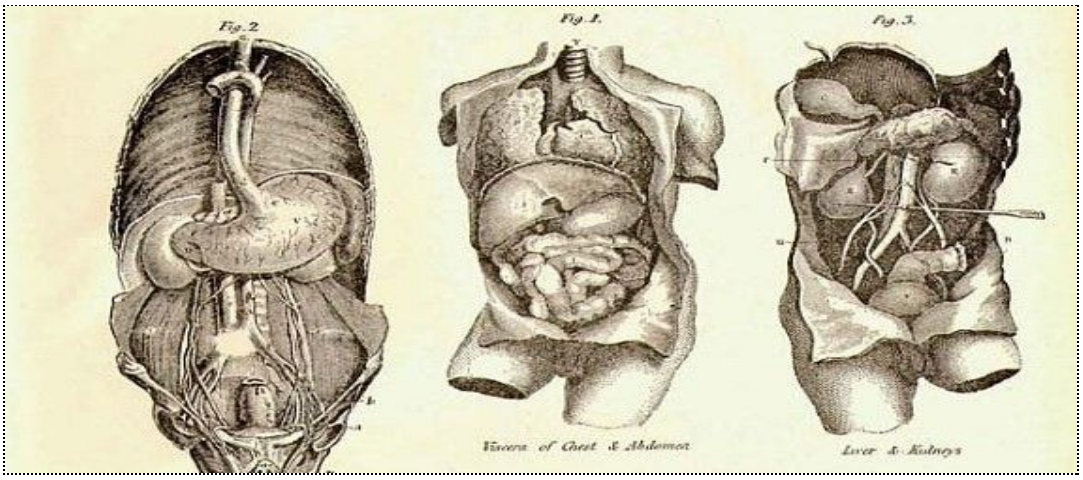
[16] التجارب التي تجرى خارج جسم الإنسان في المعمل
[17] التجارب التي تجرى داخل جسم الانسان
[18] لانه رخيص وفي متناول اليد فصاروا يستخدمونه دائما مما أدى إلى مقاومة البكتيريا لهذا الدواء.
[19] الفكرة اننا نبدأ نعطي المريض triple therapies ونخليه يستمر عليها لمدة اسبوع ,اذا بعد اسبوع ماتحسن نعطيه quadruple therapies حيث انها اقوى تأثير لكن مشكلتها كثرة أعراضها الجانبية
[20] you have to choose one of them after doing the resistance test
[21] Acts as antimicrobial & protects ulcer surface
[22] 4 times a day
[23] المقصد انه اهم دواء بال quadraple therapies هو bismuth بدونه ماراح تنفع هالكومبنيشن ولا راح تعطي تأثير ,فإذا bismuth غير متوفر ارجع لل triple therapies احسن.
[24] Due to clostridium.difficile

# SUMMARY

<table>
<tr><th colspan="3">Helicobacter pylori</th></tr>
<tr><td rowspan="2">Description</td><td>Morphology</td><td>Gram-negative,spiral rods, motile by polar flagella.</td></tr>
<tr><td>Fastidious in terms of growth requirements</td><td>strictly microaerophilic require C02 for growth/charcoal on chocolate agar medium</td></tr>
<tr><td>Pathophysiology</td><td colspan="2">H. pylori colonizes gastric mucosal cells in the stomach, surviving in the mucous layer that coats the epithelium. The organism is noninvasive, but recruits and activates inflammatory cells, thus causing a chronic inflammation of the mucosa. H. pylori secretes urease, producing ammonium ions that neutralize stomach acid in the vicinity of the organism, thus favoring bacterial multiplication. Ammonia can damage the gastric mucosa, and may also potentiate the effects of a cytotoxin produced by H. pylori</td></tr>
<tr><td>Laboratory characteristic</td><td colspan="2">Hallmark of the species is production of <u>urease enzyme</u><br>Catalase-positive/Oxidase-positive.</td></tr>
<tr><td rowspan="2">Diagnosis</td><td>Noninvasive</td><td>Blood antibody test (IgG, IgM or IgA)-Stool antigen test-Carbon urea breath test (C14 or C13 )</td></tr>
<tr><td>Invasive</td><td>Endoscopy followed by culturing the bacteria-Histology-CLO test</td></tr>
<tr><td>Epidemiology</td><td colspan="2">More in: childhood ,developing countries ,poor sanitation</td></tr>
<tr><td>Transmission</td><td colspan="2">unknown, although it is known individuals typically become infected in childhood.<br>They believe in oral- oral or fecal-oral</td></tr>
<tr><td>Prevention</td><td colspan="2">Proper sanitation and clean sources of drinking water.</td></tr>
<tr><td>Treatment</td><td colspan="2">Elimination of H. pylori requires combination therapy with two or more antimicrobials due to rapid appearance of resistant strains.<br>First line(Triple): PPI+ Clarithromycin + Amoxicillin (or metronidazole)<br>2nd line(quadruple): PPI + bismuth subsalicylate/subcitrate+Metronidazole +Tetracycline<br>Or<br>PPI+ Ranitidine Bismuth Citrate +Amoxycillin + metronidazole</td></tr>
</table>




إِنَّا كُلَّ شَيْءٍ خَلَقْنَاهُ بِقَدَرٍ ﴿٤٩﴾

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