جامعة الملك سعود
King Saud University
1957

Role of *H.pylori* in Peptic Ulcer and Drugs Used in Treatment

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Objectives

- At the end of the lectures students should be able to:
  - Explain the various gastric and duodenal diseases caused by *H.pylori*.
  - Discuss the epidemiology and transmission of *H. pylori*.
  - Describe the pathophysiology of *H.pylori* inside the stomach and duodenum.
  - Define peptic ulcer disease and assess its distribution among patients.
  - Indicate the signs and symptoms of associated disease.

Continue: objectives

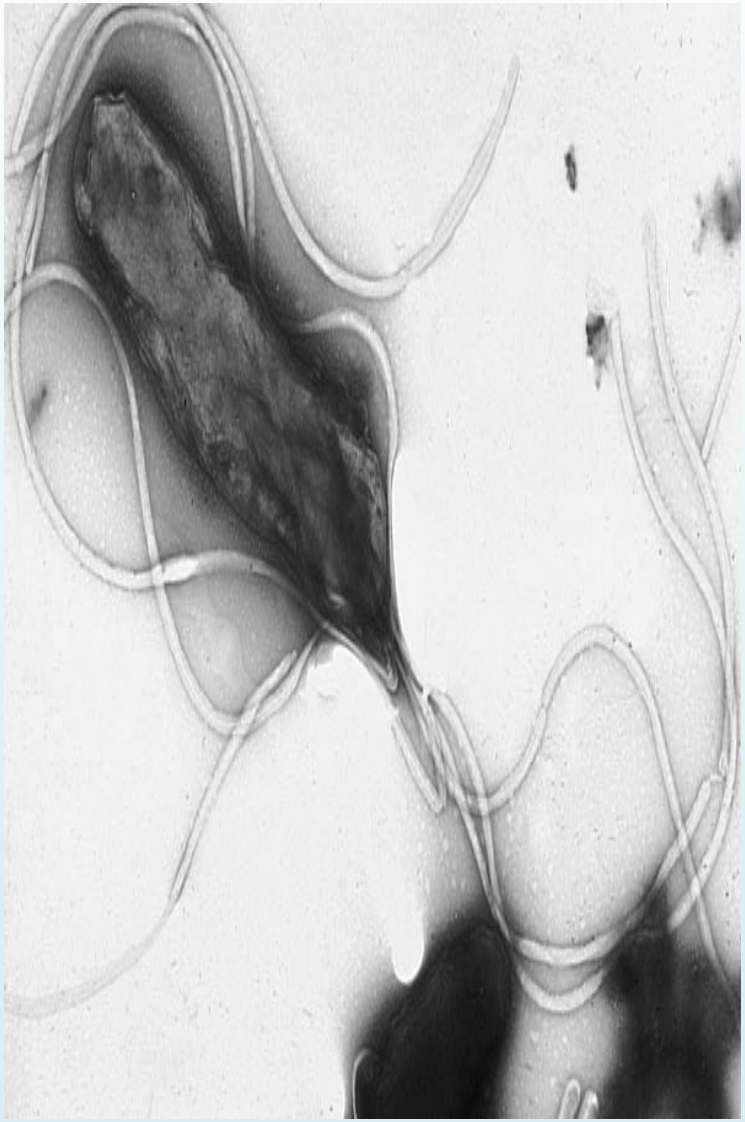
- Discuss the impact of the discovery of *H.pylori* on the change of diagnosis and management of peptic ulcer.
- Describe laboratory characteristics of *H. pylori*, its identification and diagnosis.
- Discuss preventative methods used for *H. pylori* infection.
- Describe the management and treatment regiments used for eradication of *H. pylori*.

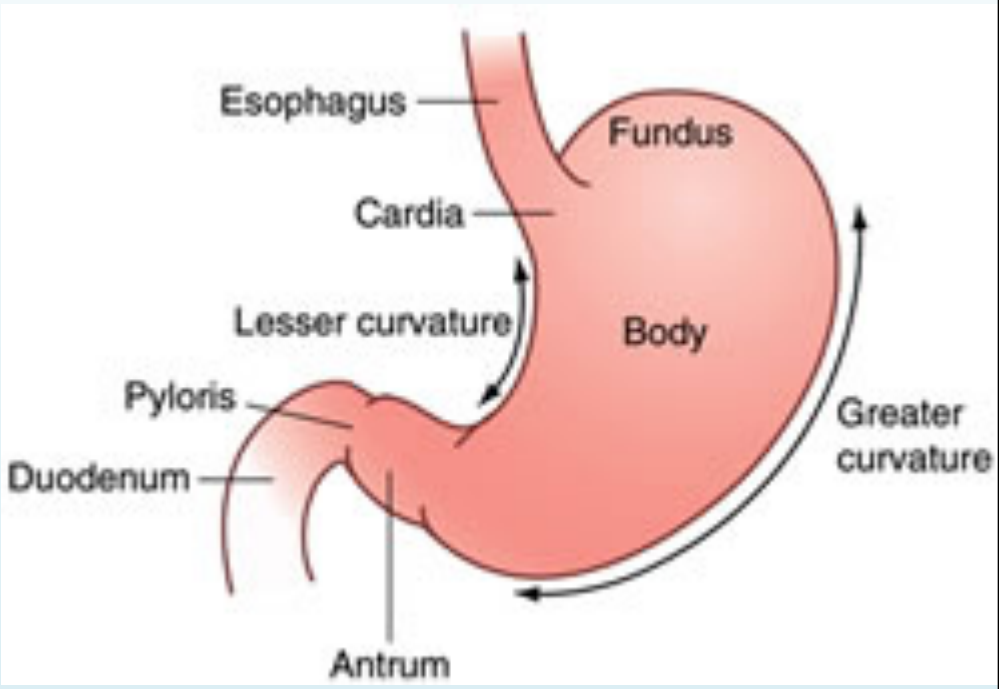
Helicobacter pylori

- 1983 in Perth (Australia),Warren and Marshal.
- Discovery revolutionised the treatment of duodenal and gastric ulcers.
- Earned them the Nobel Prize for Medicine in 2005.
- Nearly 20 species of *Helicobacter* are now recognised.
- *H. pylori* are found in the human stomach.
- There is no evidence of animal-to-human transmission

Helicobacter pylori

- *Helicobacter pylori* is found closely associated with gastric mucosa and is an independent risk factor for the development of:
  - chronic active gastritis
  - gastric and duodenal ulcer (Peptic ulcer)
  - Gasric adenocarcinoma
  - Gastric mucosa-associated lymphoid tissue (MALT) lymphoma.




Esophagus
Fundus
Cardia
Lesser curvature
Body
Pyloris
Greater curvature
Duodenum
Antrum

Epidemiology

- Around **50%** of world's population harbor *H pylori*.
- **Third world** has more rate of infection.
- Infections are usually **acquired at childhood**.
- **Poor sanitary** conditions contribute to **high** rates.
- In USA high prevalence among **African-American** and **Hispanic** population, due to **socioeconomic** status.
- **Higher hygiene** standards and widespread use of **antibiotics** behind lower rate of infection in the west.
- Overall frequency of *H pylori* infection is **declining**.

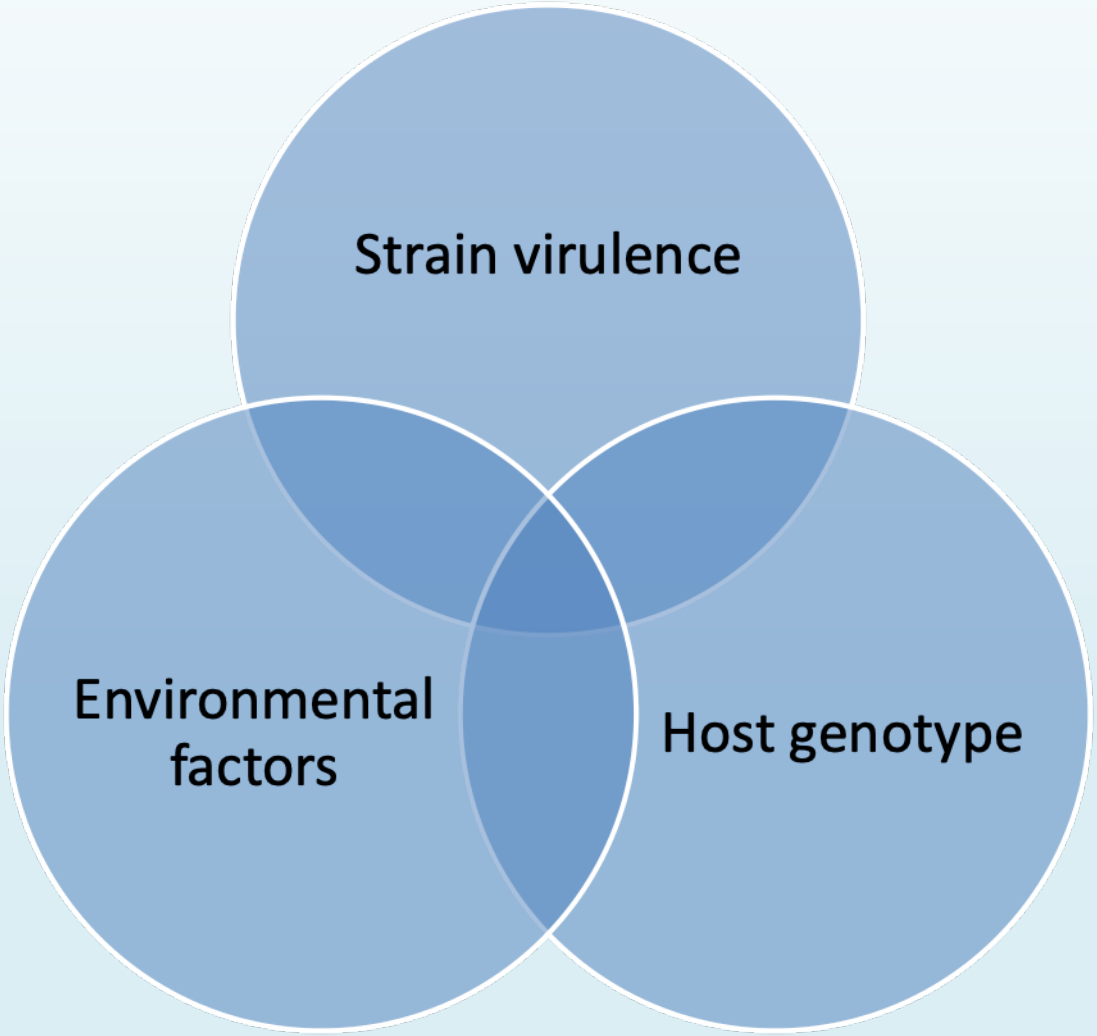
Epidemiology

- Over 80% of individuals infected with the bacterium are asymptomatic.
- Prevalence varies greatly among countries and population groups.
- Infection is more prevalent in developing countries.
- The route of transmission is unknown, although it is known individuals typically become infected in childhood.

Transmission

- **Contagious** with an unknown route of transmission .
- **Person to person** (oral to oral or fecal-oral) route.
- **Transmission** occur mainly within families or community.
- **Fecal-oral** route of infection occur by ingestion contaminated food or water due poor hygiene.
- Using same spoons, forks and tooth brushes and kissing children mouth to mouth increases oral-oral route of infection.
- Gastric antrum is the most favoured site.
- Present in the mucus that overlies the mucosa.

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



Genome

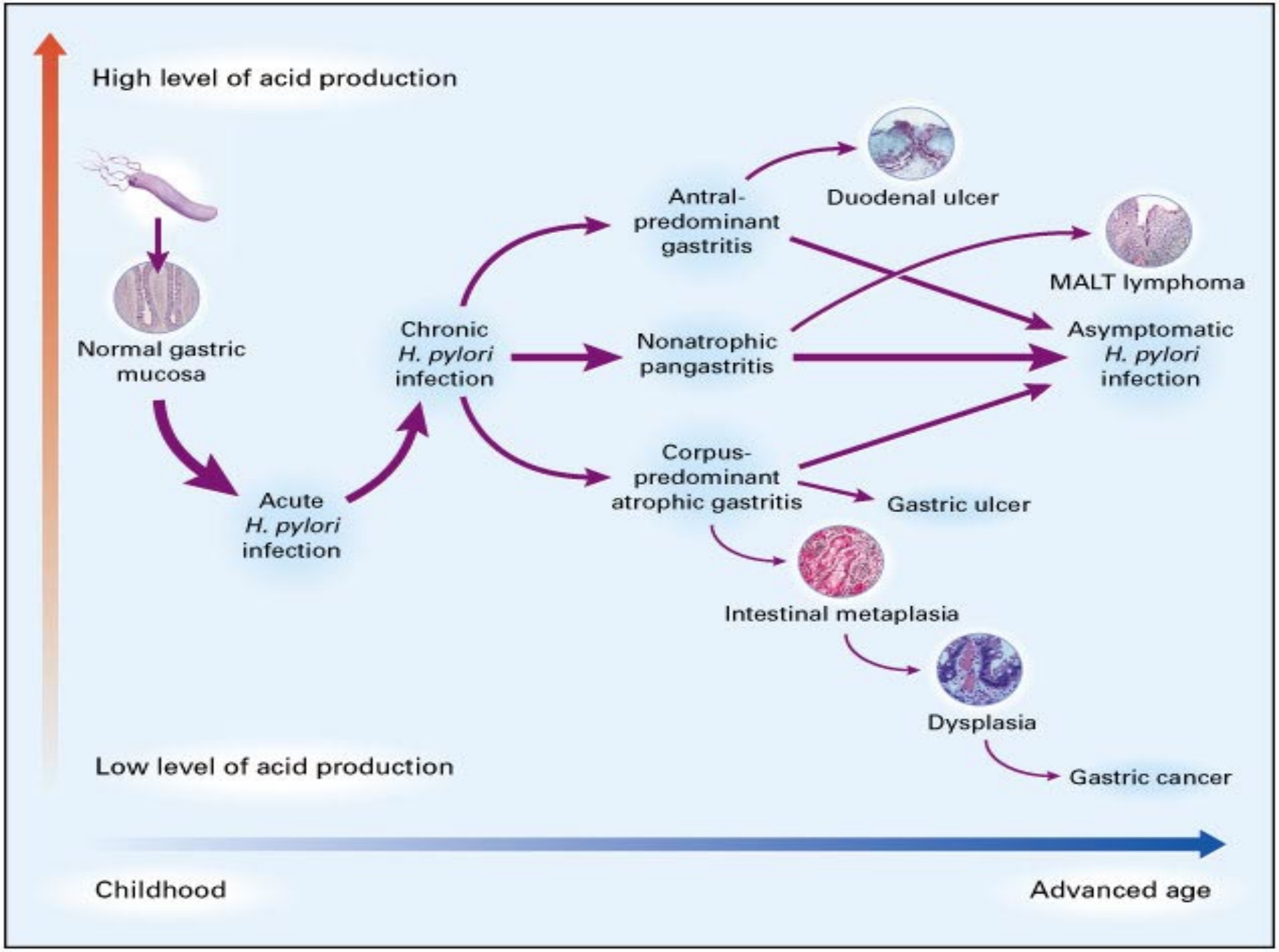
- *H pylori* consist of large diversity of strains with around 1,550 genes.
- Study of *H pylori* is centered on trying to understand the **pathogenesis of genome** database.
- *H pylori* contain 40kb-long Cag pathogenicity island (PAI) with over 40 pathogenetic genes.
- **Asymptomatic** patients carry *H pylori* strains lacking the Cag pathogenesity island (PAI).

Pathophysiology

- To **colonize** the stomach, *H pylori* must survive acidity.
- Using flagella, *H pylori* moves through stomach lumen and drill into the mucoid lining of stomach.
- Produces adhesions (outer membrane proteins) that binds to the epithelial cells.
- Produces large amounts of *urease* enzyme that break down urea into co2 +ammonia.
- This in-turn **neutralizes** gastric acid.
- Ammonia is toxic to epithelial cells along with *proteases*, *vacA* protein and *phospholipases* produced by *H pylori* and could damage epithelial cells.

Pathophysiology- cont

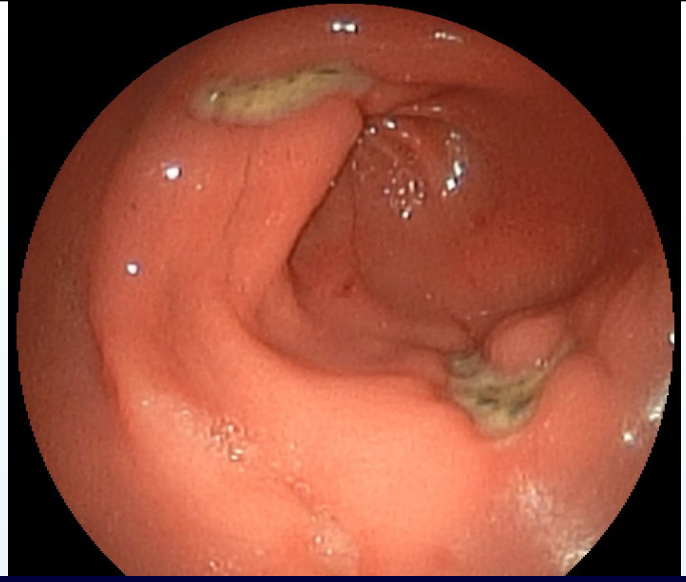
- Colonization of stomach or duodenum can result in chronic gastritis (inflammation of stomach lining).
- Inflammation stimulate more production of gastric acid.
- This leads to gastric and duodenal ulcers, atrophy and later cancer.
- CagA protein was found to contribute to peptic ulcer.
- Neutrophil-Activating 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.

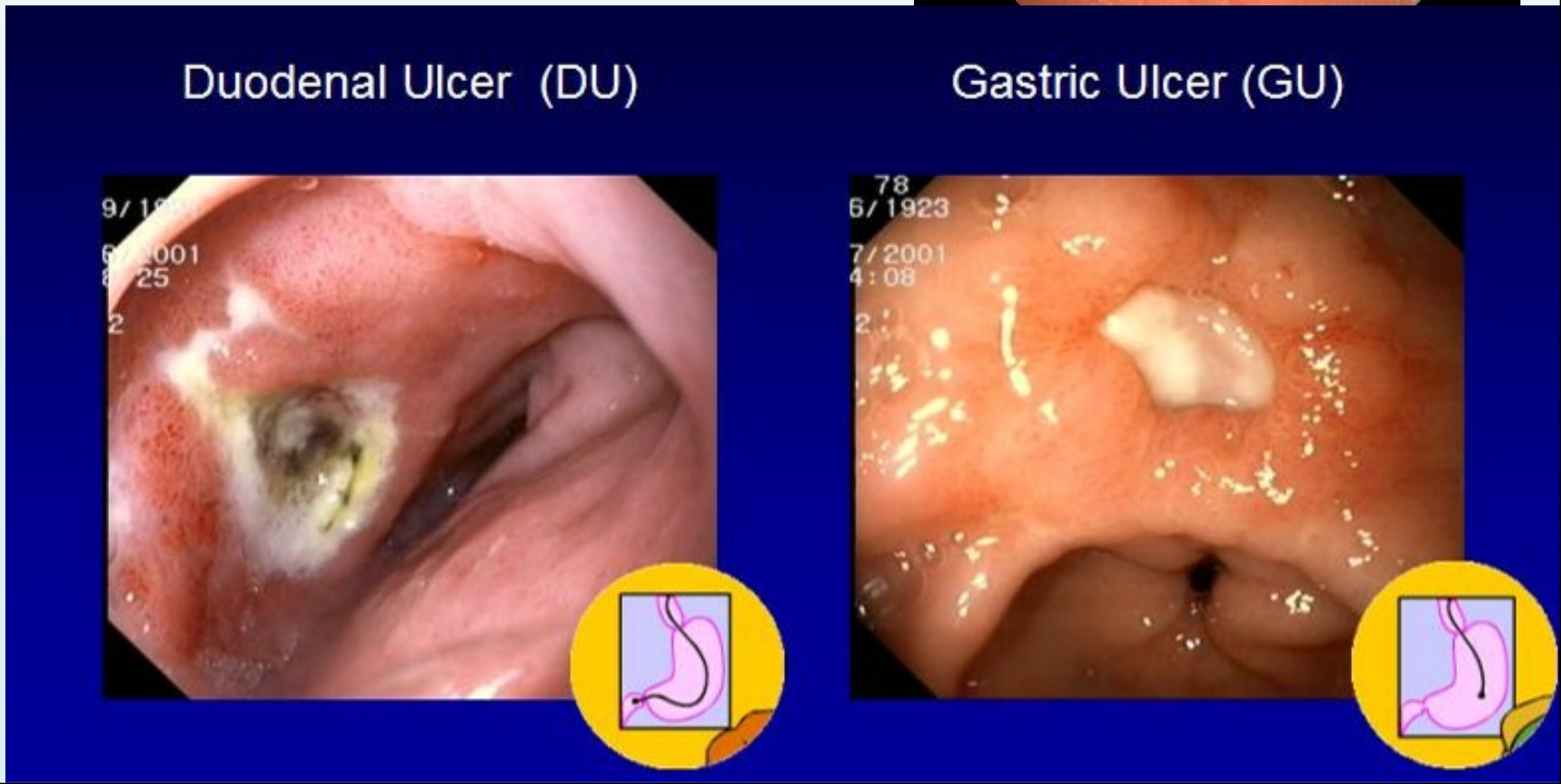

High level of acid production
Normal gastric mucosa
Acute *H. pylori* infection
Chronic *H. pylori* infection
Antral-predominant gastritis
Duodenal ulcer
Nonatrophic pangastritis
MALT lymphoma
Asymptomatic *H. pylori* infection
Corpus-predominant atrophic gastritis
Gastric ulcer
Intestinal metaplasia
Dysplasia
Gastric cancer
Low level of acid production
Childhood
Advanced age

Peptic ulcer

- **Peptic ulcer disease (PUD):**
  - Mucosal erosions(≥ 0.5cm)
  - *H. pylori* infection is the main cause
  - Associated with the over usage of NSAIDs, smocking, alchohol
  - Peptic ulcer is created in an acidic area (very painful).
  - More Peptic ulcers arise in duodenum than stomach.
  - 4% of stomach ulcer can turn to be malignant tumor.
  - Duodenal ulcers are generally benign.
  - Multiple biopsies are needed to exclude cancer.

Peptic ulcer images





Signs and symptoms

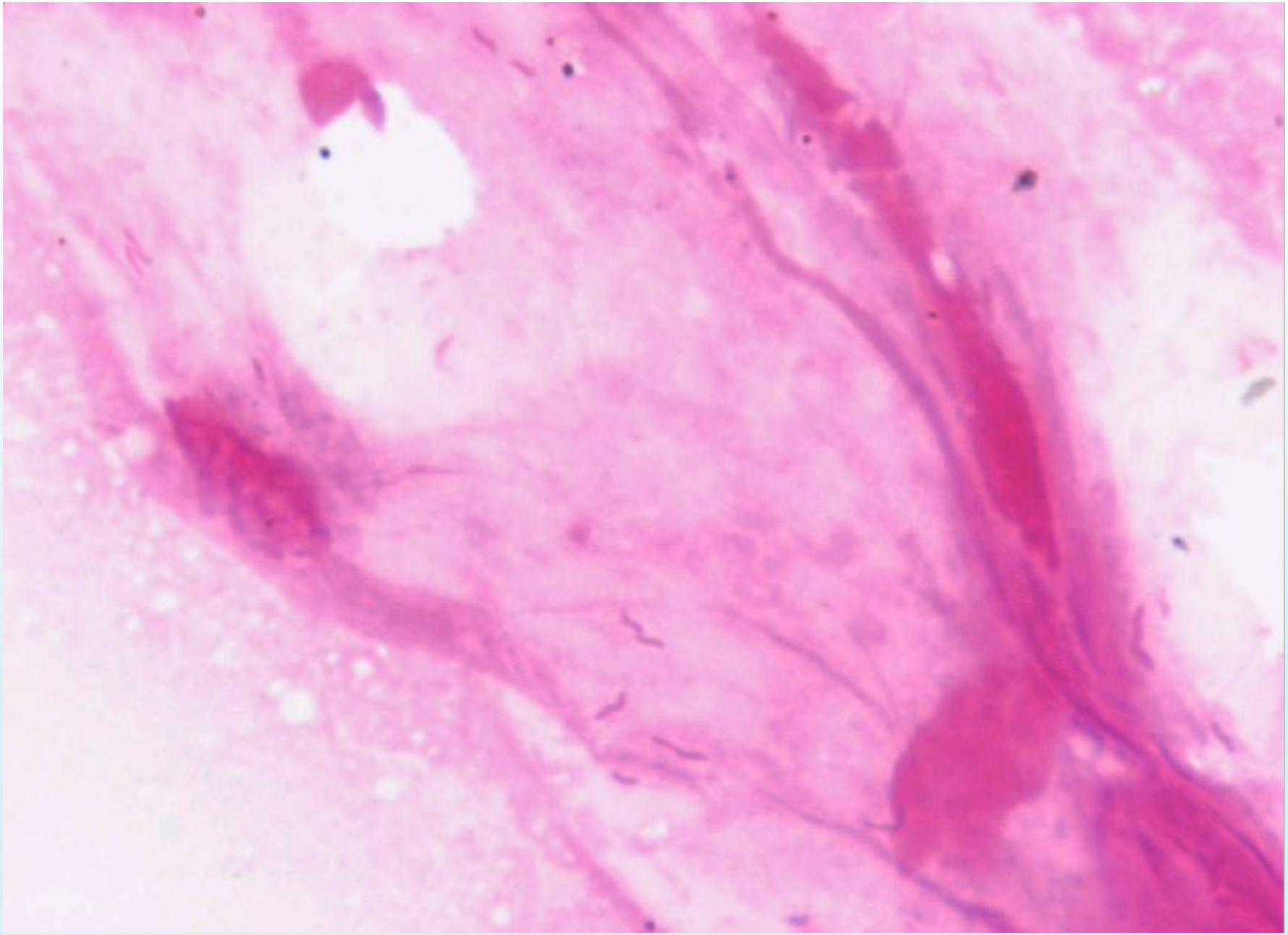
- Abdominal pain, epigastric with severity relating to mealtime (3 hours after meal with gastric ulcer).
- Bloating and abdominal fullness.
- Nausea and vomiting.
- Loss of appetite and weight loss.
- Haematemesis (vomiting of blood) due to gastric or esophagus damage.
- Melena (foul-smelling & dark brown faeces due to oxidized hemoglobin iron.
- Rarely, Gastric or duodenal perforation leading to acute peritonitis (extremely painful-require urgent surgery.

Description

- Gram-negative spiral bacillus
- Fastidious in terms of growth requirements
  - Strictly microaerophilic
  - Will grow in environments with increased Co2
  - Blood agar based medium
- **Morphology and staining**
  - Small, Gram-negative, spiral rods, motile by polar flagella.

Laboratory characteristics

- **Culture**:
  - On blood agar based medium in a moist microaerophilic atmosphere.
  - Selective medium can be used for isolation from clinical specimens
  - Small colonies grow after 5-7 days at 37˚C.
- **Biochemical reactions**: catalase-positive; oxidase-positive; strongly urease-positive.



- Hallmark of the species is production of urease enzyme
  - Urease breaks urea down to Co2+NH3
  - Amonia is a strong base
  - Urease helps *H. pylori* survive strongly acidic stomach conditions.

- Very fragile (a point of importance when referring samples to the lab)

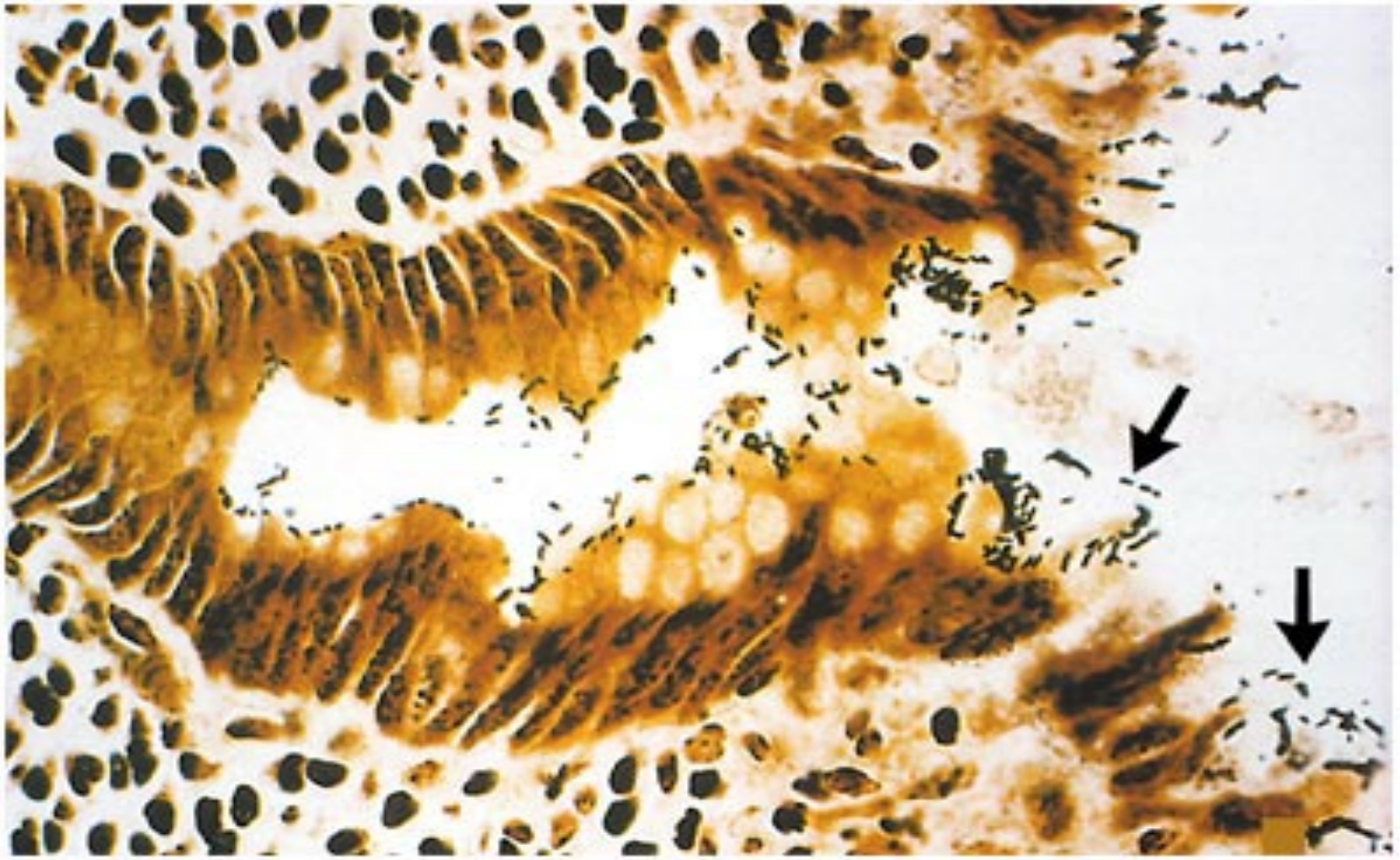
Diagnosis

- Checking **dyspeptic patients** for *H pylori*.
- **Non-invasive methods:**
  - **Serology** (Blood antibody) tests
    - poor accuracy
  - **Stool antigen test**.
  - **Carbon urea breath** test (**C^{14}** or **C^{13}).**
    - a urea solution labelled with C14 isotope is given to pt. The Co2 subsequently exhaled by the pt contains the C14 isotope and this is measured. A high reading indicates presence of *H. Pylori.*

Invasive methods

- **Invasive methods (most reliable), on biopsy:**
  - **Histological** examination of biopsy specimens of gastric/duodenal mucosa take at endoscopy.
  - **Rapid urease test (CLO-test ®)** : based again on urease-production by the organism->NH3 production->rise in pH=>change in the colour indicator of the kit
    - High sensitivity and specificity-
    - Prompt result.
  - **Culturing** the bacteria. Used for antibiotic resistance testing, as sensitive as the histology. Requires selective agars and incubation for growth.
  - **Molecular** methods (e.g. PCR)

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



Prevention

- **Treatment and eradication of infection will**
  - Improve symptoms
    - Such as (dyspepsia, gastritis, peptic ulcer and cancer).
  - Potentially reverse progression
- **Vaccination:**
  - Promising results with newer formulations
  - No vaccine available yet
- **Dietary methods:** (eating broccoli, cabbage, honey, and drinking green tea).
- **Proper sanitation and clean sources of drinking water).**

Antibiotic sensitivity

- **In vitro** *H.pylori* is sensitive to amoxycillin, tetracycline, metronidazole, macrolides (clarithromycin).
- However, **in vivo** 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%).

Treatment Regimens

- **Different options include:**

- **Clarithromycin triple therapy**
  - PPI b.d. (twice a day) + clarithromycin
  - + amoxicillin **or** metronidazole for 14 days

- **Bismuth quadruple therapy**
  - PPI b.d. + bismuth subsalicylate/subcitrate + metronidazole + tetracycline for 10 - 14
  - Can be used as salvage therapy if primary therapy with the Clarithromycin triple therapy fails
  - Another option for salvage:
    - levofloxacin + amoxicillin + PPI

Chey, W. D., Leontiadis, G. I., Howden, C. W., & Moss, S. F. (2017). ACG clinical guideline: treatment of Helicobacter pylori infection. *The American journal of gastroenterology*, 112(2), 212-239.

Post Treatment Testing

- After identification and treatment, eradication should be proven using:
  - Urea breath test
  - Fecal antigen test or
  - Biopsy based testing

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Susceptibility Testing

- Not available in all centers
- Require growth from culture, so biopsy needed
- More recently molecular methods looking for mutations that code for resistance have been used

Reference book

- ***Sherries*** **Medical Microbiology, an Introduction to Infectious Diseases.** Latest edition, Kenneth Ryan and C.George Ray. Publisher : McGraw Hill .

  Chapter 32