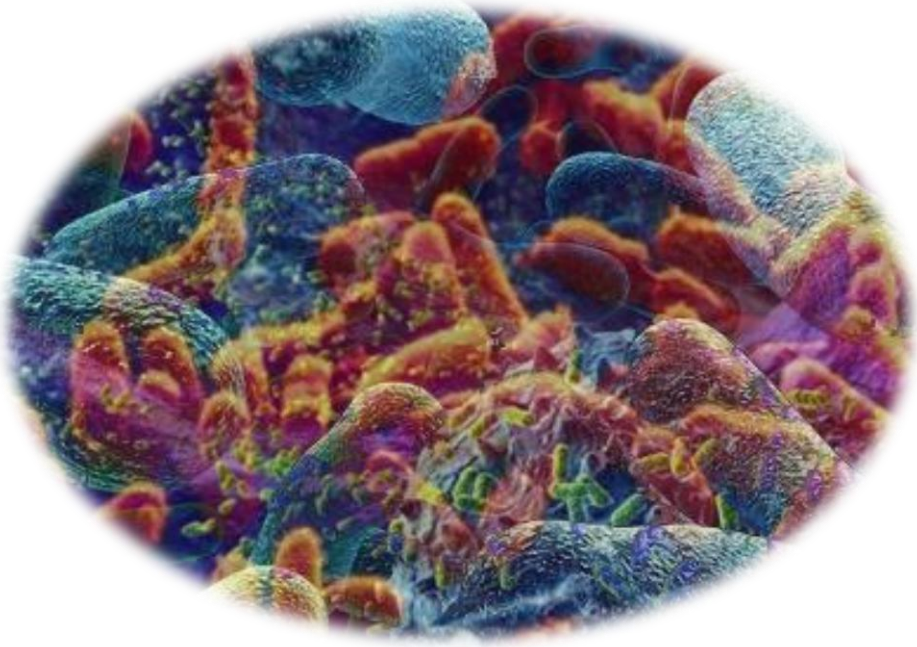
431 Microbiology Team

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

GIT & HAEMATOLOGY BLOCK



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Peptic Ulcer Disease:

Is an ulcer define as mucosal erosions (≥ 0.5cm) associated with the over usage of NSAIDs. (That's what written in the Slides, which is different than any other source).

- Peptic ulcer is created in an acidic area (very painful).
- **More Peptic ulcers are 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.

Signs and Symptoms:

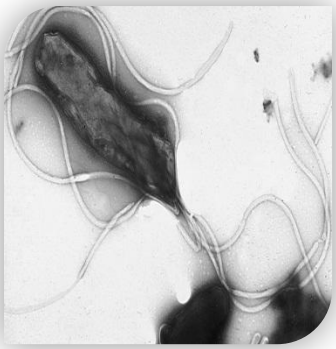
- Abdominal pain, epigastric with **severity relating to mealtime (3 hours after meal with gastric ulcer).**
- Bloating and abdominal fullness.
- Nausea and vomiting.
- Loss of appetite and weight loss.
- Haematemesis (vomiting of blood) due to gastric or esophagus damage.
- Melena (foul-smelling dark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

Old Management:

- Previously every surgeon faced with a perforated peptic ulcer had to open the abdomen, sewing up the hole, and avoiding inflammation with cleansing abdomen cavity.
- Perforated peptic ulcer was a dangerous associated with high morbidity and mortality.
- Gastrectomy (where part of the stomach or all is resected) is no longer used for peptic ulcer management.

In a nutshell: Old management = surgery

Helicobacter pylori:



- 1982 in Perth (Australia), Warren and Marshal.
- Helicobacter pylori (formerly known as Campylobacter.pylori or C.pyloridis) is found closely associated with gastric mucosa and causes **chronic active gastritis, gastric and duodenal ulcer (Peptic ulcer) and could develop adenocarcinoma**.
- H.pylori plays a role in gastric and duodenal ulceration and probably also gastric cancer. Over 80% of individuals infected with the bacterium are **asymptomatic**.(We'll discuss it later).
- More than 50% of the world's population harbour H. pylori in their **upper gastrointestinal tract**. Infection is more prevalent **in developing countries**.
- The route of transmission is unknown, **although it is known individuals typically become infected in childhood.**

Laboratory Characteristics	**Morphology and staining**	**Small, Gram-negative, spiral rods, motile by polar flagella.** (imp!)
	Culture	On blood or chocolate agar in **a moist microaerophilic atmosphere**. For isolation from clinical specimens, use campylobacter selective medium. Small colonies grow after 3-7 days at 37˚C. (Slow growing Organism)
	Biochemical reactions	**catalase-positive, oxidase-positive, strongly urease-positive**. (imp!)
	Typing	a variety of nucleic acid methods have been developed, but there is no agreed typing scheme.
	Serology	looking for IgG and IgM to Cytotoxic Associated Gene A (**CagA**) and (**VacA**) for virulence strains.

Diagnosis

- Checking for dyspeptic patients for H pylori. By either:

Non-invasive methods	Invasive methods **(most reliable)**
Blood antibody test (IgG, IgM or IgA) Stool antigen test. **Carbon urea breath test (C14 or C13).**	Endoscopy followed by Histological examination. **Endoscopy followed by culturing the bacteria**.

Genome

- H pylori consist of large diversity of strains with 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.
- **The cagA gene codes for the major H pylori virulence proteins.** (imp!)
- 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 that binds to the epithelial cells.
- **Produces large amounts of urease enzyme that break down urea into CO_2 + ammonia.**
- This in-turn neutalizes gastric acid.
- **Ammonia is toxic to epithelial cells along with proteases, vacA protein and phospholipases produced by H pylori and could damage epithelial cells.**
- 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.**
- **CagA protein was found to contribute to peptic ulcer.**
- **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 6** that leads to host cells **mutation** → leading to cancer.

Prevention:

- Eradication of infection will improve symptoms: Such as (dyspepsia, gastritis, peptic ulcer and cancer).
- **Vaccination:**
  - Promising results with studying adjuvant, antigens.
  - Determining route of immunization (oral or intramuscular).
- Dietary methods: (eating broccoli, cabbage, honey, and drinking green tea).
- Proper sanitation and clean sources of drinking water.

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.
- **Recently, antibiotics (metronidazole, clarithromycin) are becoming resistance to H pylori.**
- **Contagious** with an **unknown** route of transmission.
  - Person to person (oral to oral or fecal-oral) route.
  - Transmission occurs 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.

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%).

[Dr.Fawzia said : study the treatment from Pharma not Micro slides]

Before we go to treatment, just keep in your mind the treatment is a little bit different "or just simple" in Pharmacology, it was (Amoxicillin + Clarithromycin + Omeprazole).

Triple therapies

- **One-week combination of Omeprazole, Clarithromycin and Tinidazole the rate of eradication was 95%-100%.**
- 10 days combination of Ranitidine Bismuth citrate, Amoxycillin and Clarithromycin with eradication rate of no more than 75%.
- 10 days combination of Ranitidine Bismuth citrate, Clarithromycin and metronidazole with an eradication rate of 90%.
- **One-week combination of Omeprazole, Amoxycillin and metronidazole the rate of eradication was 96%- (very cost effective).**

Quadriple therapies

7 days regimen of combination of Amoxicillin, metronidazole, Ranitidine Bismuth Citrate and proton pump inhibitor (Omeprazole) 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** in 11% of patients.

Recommendations for treatment of H pylori infection (Maastricht III Consensus Report) 2007

- Due to Clarithromycin development of resistance, susceptibility testing is recommended pretreatment.
- Further standardization is recommended for Metronidazole before susceptibility testing is done.
- **PPI + Clarithromycin + Amoxicillin or Metronidazole treatment remains the first choice treatment if clarithromycin resistance is less than 15-20%.**→(N.B. Metronidazole is substituted to amoxicillin for patients allergic to penicillin)
- With less than 40% Metronidazole resistance prevalence PPI-Clarithromycin-metronidazole is used.
- **Bismuth-based quadruple theapies remain best second choice treatment if available.**

Summary:

- **Helicobacter Pylori is a small gram negative spiral rod, Oxidase, catalase and Urease positive.**
- **Diagnosis** : can be by ..
    - **non-invasive methods** such as **Blood anti-body**, **Stool antigen** and **Carbon Urea Breath test**.
    - Or **invasive methods** which **are more reliable** such as **endoscopy** to take a specimen and send it to **Histopathology** or for **Culture and sensitivity**.
- The **cagA** gene codes for the **major H pylori virulence proteins.**
- **Signs and symptoms:** Abdominal pain, epigastric with severity relating to meal time, bloating and abdominal fullness, loss of appetite & weight loss, nausea & vomiting , haematemesis & melena .
- Colonization of stomach or duodenum results in **chronic gastritis** which will stimulate more production of gastric acid leading to gastric and duodenal ulcers, atrophy and later cancer.
- Infections are usually acquired at **childhood.**

Questions:

(1) H.pylori is associated with which one of the following diseases :

a. Cholera
b. Peptic ulcer disease
c. Gastroenteritis
d. Bacterial dysentery

(2) Most reliable method for diagnosing H.pylori infections is :

a. Carbon urea breath test
b. Blood antibody test
c. Endoscope
d. Stool antigen test

(3) A male patient presented to the outpatient clinic complaining of abdominal pain that is epigastric with severity relating to meal time , haematemesis & melena . Using the endoscope doctor detects an ulcer and take a biopsy for laboratory examination. A biopsy identify the presence of which one of the following organisms:

a. H. pylori
b. Enteroinvasive E.coli
c. Vibrio cholera
d. Shigella species

Answers

1- b 2- c 3- a