Lecture (One)

Helicobacter pylori

Objectives:

- Not given

P.S. There are some difference between the males and females slides
The last 3 slides are the difference
+
Gray color = mentioned in the males slides but not in females

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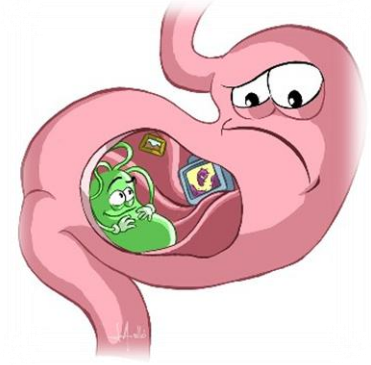
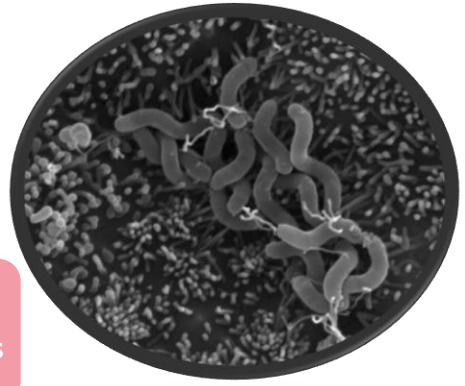
MIND MAP
(Helicobacter pylori)





- Helicobacter pylori
- **Laboratory Characteristics**
- Epidemiology
- Transmission
- Site of infection
- **Diagnosis**
- Treatment

Peptic ulcer

Peptic ulcer disease (PUD)	Is an ulcer define as **mucosal erosions (≥ 0.5cm)** associated with the over usage of NSAIDs . • 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).

Helicobacter pylori

• 1982 in Perth (Australia), Warren and Marshal.
• formerly known as Campylobacter.pylori or C.pyloridis

Directly associated with gastric mucosa and causes:

- (Peptic ulcer)
- Adenocarcinoma "Gastric carcinoma"
- gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

Over 80% of individuals infected with the bacterium are asymptomatic.

Morphology and staining	**Small, Gram-negative, spiral rods, motile by polar flagella**

Laboratory Characteristics

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.**
Biochemical reactions	**catalase-positive; oxidase-positive**; **strongly urease-positive**.
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.

Epidemiology

- Prevalence varies greatly among countries and population groups.
- 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.

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.

Site of infection

- Highly adapted organism that lives only on gastric mucosa
- Gastric antrum is the most favoured site.
- Present in the mucus that overlies the mucosa.

Diagnosis

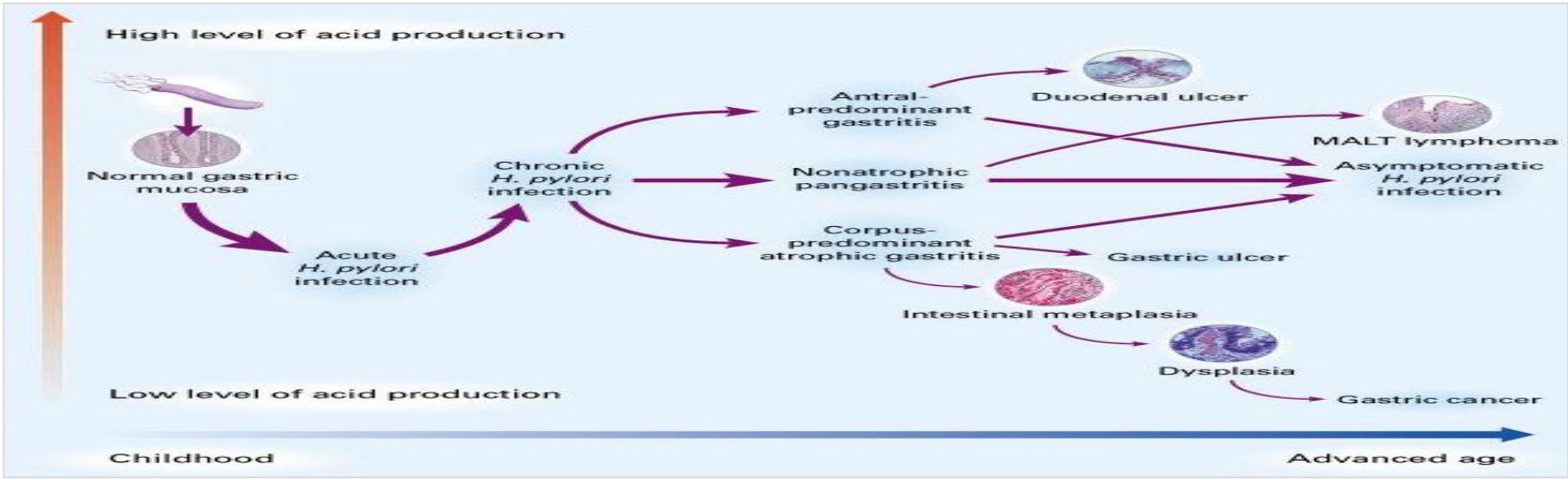
Checking for dyspeptic patients for *H pylori*.

Non-invasive methods	Invasive methods(most reliable):
•**Carbon urea breath test (C14 or C13)** 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* •**Polymerase chain reaction (PCR)** •Serology: (ELISA) Blood antibody test (poor accuracy) •**Stool antigen test.**	• **Endoscopy followed by Histological examination**: **CLO-test:** "Campylobacter-like organism 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 • **Endoscopy followed by culturing the bacteria.** - used for antibiotic resistance testing, as sensitive as the histology - requires selective agars and incubation periods

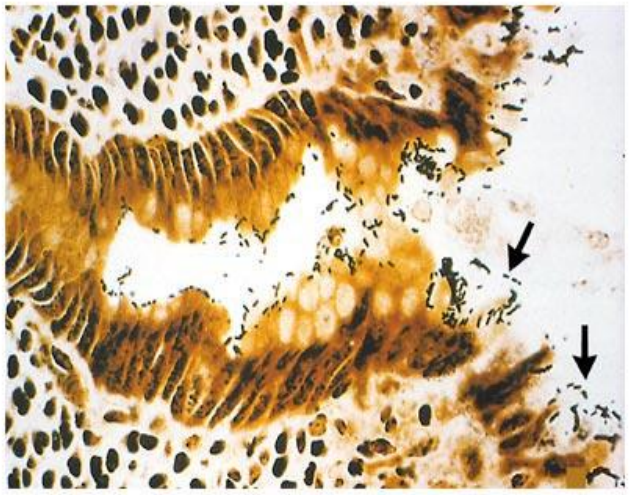
Treatment

Important

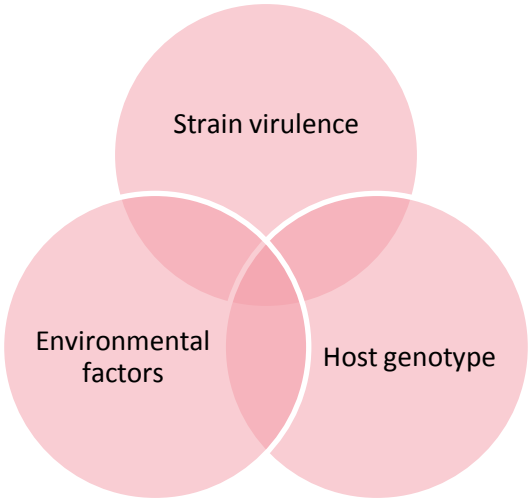
First line therapy	PPI b.d. + clarithromycin 500mg b.d. +amoxicillin 1000mg b.d. or (metronidazole 400mg BD) minimum of 7 days In case of failure we use the second line therapy
Second line therapy	PPI b.d. + bismuth subsalicylate/subcitrate 120mg QDS + metronidazole 500mg t.d.s. + tetracycline 500mg q.d.s. for a minimum of 7 days ▪ If bismuth is not available, PPI based triple therapies should be used ▪ Subsequent failures should be handled on a case-case basis. Patients failing second-line therapy in primary care should be referred



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



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



Path physiology	• 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 co2 + 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 8** that leads to host cells mutation .
Prevention:	Eradication of infection will improve symptoms: Such as (dyspepsia, gastritis, peptic ulcer and cancer). Vaccination: Promising results with **studying <u>adjuvant, antigens</u>**. Determining **<u>route of immunization</u>** (oral or intramuscular). Dietary methods: (eating broccoli, cabbage, honey, and drinking green tea). Proper sanitation and clean sources of drinking water).

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**.
Asymptomatic patients carry H pylori strains lacking the Cag pathogenesity island (PAI).

Boys slides

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%).
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).
Quadruple 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%. With less than 40% Metronidazole resistance prevalence PPI-Clarithromycin-metronidazole is used. Bismuth-based quadruple theapies remain best second choice treatment if available.	

Females slide

Course of infection	After several days incubation period, **patients suffer mild attack of acute gastritis:** **- abdominal pain -nausea - flatulence -bad breath** Symptoms last about 2/52 but hypochlorhydria can last up to one year • Despite a substantial antibiotic response, infection and chronic gastritis persist • After decades there *may* be progression to **atrophic gastritis** (conditions which are inhospitable for the bacteria) and numbers reduce	
Indications for therapy	**Strongly recommended**	-Duodenal or gastric ulcer -MALT lymphoma -Atrophic gastritis - Recent resection of gastric cancer
	Treatment advised	• Functional dyspepsia • Gastro-oesophageal reflux disease (patients requiring long-term acid suppressive therapy) • Use of NSAIDs
Treatment	Goal of treatment to eradicate infection ❖ Triple therapy regimens consist of one anti-secretory agent and two antimicrobial agents for 7 to 14 days ❖ Triple therapy regimens must ❖ have cure rate of approximately 80% ❖ be without major side effects ❖ minimal induction of resistance	
factors may result in failure of treatment	❖ microbial factors ❖ patient compliance ❖ geographical differences	

Summary

- **Helicobacter Pylori** is a small gram negative spiral rod, Oxidase, catalase and **Urease positive**.
- Fastidious in terms of growth requirements is **strictly micro-aerophilic** ,require C02 for growth , on charcoal medium
- **Hallmark** of the species is production of **urease enzyme**
- urease breaks urea down to C02+NH3 , amonia is a strong base
- The process that helps *H. pylori* to survive is the strongly acidic stomach conditions.
- 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.
- 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 .
- **Infections** are usually acquired at childhood.

QUESTIONS

Q1) **Lymphoma associated with H. Pylori infection is**
a. Lymphoblastoma
b. MALT Lymphoma
c. Burkitt's lymphoma
d. Follicular lymphoma

Q2) **Peptic ulcers are caused by:**
(a) Shigella sonei
(b) Helicobacter pylori
(c) Giardia lamblia
(d) Enterobius vermicularis

Q3)Most reliable method for diagnosing H.pylori infections is :
a. Carbon urea breath test
b. Blood antibody test
c. Endoscope
d. Stool antigen test

Q4.**Helicobacter Pylori (H.Pylori) is a known cause of peptic ulcer disease. It was discovered in Australia in 1987.**
Which of the following statements is not true regarding it?
a) Its infectivity is highest in developed world.
b) Person to person transmission is common
c) It is seen in populations with low socio economic status
d)H. Pylori is a gram negative microaerophilic bacteria

1	B
2	B
3	C
4	A

H Pylori Breath Test :
http://www.youtube.com/watch?v=12AMJTSZN7s&feature=youtu.be
Test your knowledge:
http://cme.medcomasia.com/cme_symposium/mcq.asp?id=490&yr=2007&m=&d=

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