-جرثومة المعدة-

HELICOBACTER PYLORI

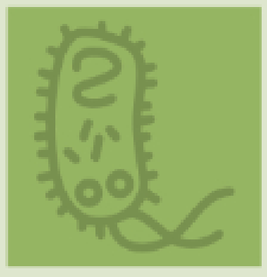
H PYLORI & DRUGS USED IN TREATMENT

Peptic Ulcer Diseases

Definition	Is an ulcer defined as mucosal erosions(≥ 0.5cm) associated with the over usage of NSAIDs , alcohol , smoking , helicobacter pylori .
Location	- Peptic ulcer is created in an acidic area. - More Peptic ulcers are arise in duodenum than stomach.
Complication	- 4% of stomach ulcer can turn to be malignant tumor. - Duodenal ulcers are generally benign. (Rarely become cancer) - (Multiple biopsies are needed to exclude cancer)
Signs & Symptoms	- Abdominal , epigastric (burning) pain with severity relating to meal time (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 feces due to oxidized hemoglobin iron). Melena only if gastric ulcer - Rarely, Gastric or duodenal perforation leading to acute peritonitis.(extremely painful require urgent surgery)

Helicobacter Pylori

General info.	- 1983 in Perth (Australia), Warren and Marshal. - Helicobacter pylori is found closely associated with gastric mucosa and is an independent risk factor for the development of: 1) chronic active gastritis 2) gastric and duodenal ulcer (Peptic ulcer) 3) gastric adenocarcinoma 4) Gastric mucosa-associated lymphoid tissue (MALT) lymphoma. - H. pylori are found in the human stomach. - There is no evidence of animal-to-human transmission - 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

Helicobacter Pylori

Epidemiology

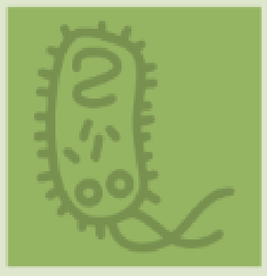
- More than 50% of the world's population harbour H. pylori in their upper gastrointestinal tract
- Third world has more rate of infection.
- Infections are usually acquired at childhood.
- Poor sanitary conditions contribute to high rates.
- In USA high prevalence among African-American and Hispanic 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.
- 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.
- Over 80% of individuals infected with the bacterium are asymptomatic.

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.

Prevention

- **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.

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

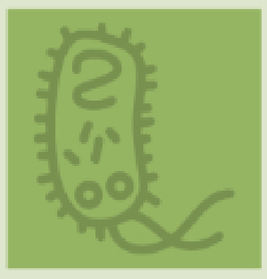
Strain virulence → Environmental factors → Host genotype

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 pathogenicity island (PAI).

Pathogenesis

- 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 neutralizes gastric acid. Very dangrouse
- 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. CagA is what makes H.pylori potentially cancerous
- 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.

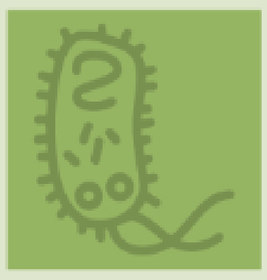



Laboratory Characteristics

Morphology	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(bacilli) , motile by flagella . - Strictly Microaerophilic
Culture	- On blood or chocolate 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 ➔Ammonia 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

Non-invasive Methods:	- **Serology (Blood antibody) tests →** poor accuracy - **Stool antigen test.** - **Carbon urea breath test (C14 or C13).** A urea solution labelled with C14 isotope is given to pt. The Co2 subsequently exhaled by the patient contains the C14 isotope and this is measured. A high reading indicates presence of H. Pylori.
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)

Antibiotic Sensitivity:

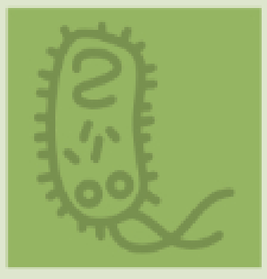
- In vitro H.pylori is sensitive to amoxicillin, tetracycline, metronidazole, macrolides (clarithromycin).
- In vivo their efficacy is often poor due to the low pH of the stomach, their failure to penetrate the gastric mucus and the low concentration of antibiotic obtained in the mucosa of the stomach.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

Tratement	
Clarithromycin Triple therapies (first line):	Bismuth Quadruple Therapies (second line):
•PPI b.d. (twice a day) + clarithromycin + amoxicillin or metronidazole for 14 days We give metronidazole if patient is allergic to Penicillin (Amoxicillin).	•PPI b.d. + bismuth subsalicylate/subcitrate + metronidazole + tetracycline for 10-14 days. -Can be used as salvage therapy if primary therapy with the Clarithromycin triple therapy fails .
Another option for salvage: levofloxacin + amoxicillin + PPI	
Post Treatment Testing : After identification and treatment, eradication should be proven using: • Urea breath test • Fecal (stool) antigen test • Biopsy based testing (usually not used)	

Susceptibility Testing: (Doctor didn't even read it

- 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.

-Vivo : in human body
-Vitro : in tube (Labs)

summary :

<table>
<tr><td>H. Pylori</td><td colspan="2">Gram-negative spiral bacilli, Strictly Microaerophilic.
Fastidious in terms of growth requirements.</td></tr>
<tr><td>Risk Factor For</td><td colspan="2">a) chronic active gastritis
b) gastric and duodenal ulcer (Peptic ulcer)
c) Gastric adenocarcinoma
d) Gastric mucosa-associated lymphoid tissue (MALT) lymphoma.</td></tr>
<tr><td>Transmission</td><td colspan="2">a)Person to person b) Fecal-oral route by ingestion contaminated food or water due poor hygiene.
* Gastric antrum is the most favored site.</td></tr>
<tr><td>Pathogenesis</td><td colspan="2">A)Flagella (Motility)
B)Urease (break down urea into co2 +ammonia)
C)Ammonia & vacA (damage epithelial cells)
D)CagA protein (makes H.Pylori potentially cancerous)</td></tr>
<tr><td rowspan="2">Laboratory characteristics</td><td>Culture</td><td>Biochemical Reaction</td></tr>
<tr><td>• On blood or chocolate agar based medium in a moist microaerophilic atmosphere.
• grows after 5-7 days at 37℃</td><td>• catalase-positive
• oxidase- positive
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<tr><td>• Serology (poor accuracy)
• Stool antigen test.
• Carbon urea breath test (C14 or C13).</td><td>• Histological examination of biopsy
• Rapid urease test
• Culturing the bacteria.
• Molecular methods</td></tr>
<tr><td rowspan="2">Treatment</td><td>Clarithromycin triple therapy</td><td>Bismuth quadruple therapy</td></tr>
<tr><td>PPI b.d. (twice a day) + clarithromycin + amoxicillin or metronidazole for 14 days</td><td>PPI b.d. + bismuth subsalicylate/subcitrate + metronidazole + tetracycline for
10 - 14</td></tr>
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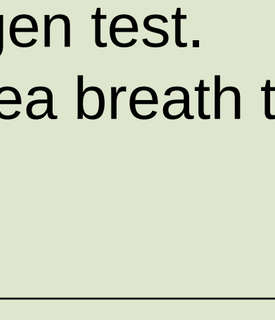
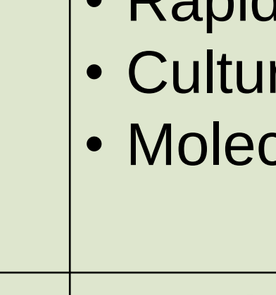
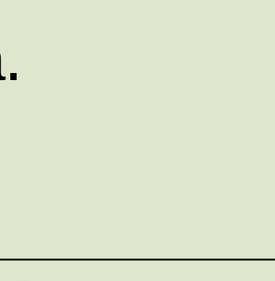




Quiz:

1. Which one of the following is false ?
   A. H.pylori is oxidase positive
   B. H.pylori is catalase positive
   C. H.pylori is urease positive
   D. H.pylori is gram positive
1. Which of the following is an invasive diagnostic method used for H.pylori?
   A.rapid urease test
   B. serology tests
   C. fecal antigen test
   D.carbon urea breath test

1. Which of the following is the treatment for a penicillin hypersensitive patient coming with H.pylori peptic Ulcer?
   A. metronidazole + azithromycin
   B.PPI +clarithromycin +amoxicillin
   C.PPI +clarithromycin +metronidazole
   D.PPI +clarithromycin +tetracycline
1. Which of the following isn't a disease caused by H.pylori?
   A.gastric adenocarcinoma
   B.gastric and duodenal ulcer
   C. MALT lymphoma
   D.acute gastritis

5. Which of the following isn't a symptom of peptic ulcer?
   A.epigastric pain
   B.melena
   C. hematemesis
   D.dry cough

CASE:A 50-year-old male visits his primary care physician complaining of upper gastric pain of extended duration. His physician administers a breath test in which radiolabeled urea is administered. Radioactive carbon dioxide was released, indicating a positive test for the pathogen shown.

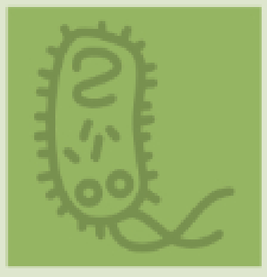
6A-What is the most likely etiology and infection?

6B-The pathogen shown is unique in its ability to colonize the stomach for extended periods of time. What virulence factor allows the bacterium shown to survive in the presence of stomach acid?

Answers:
1. D
2. A
3. C
4. D
5. D

6A: The patient most likely has a gastric ulcer caused by Helicobacter pylori .

6B: The virulence factor urease (cleaves urea to ammonia and carbon dioxide. The ammonia neutralizes the acid in the stomach, making conditions favorable for the bacterium)

THANK YOU!

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