GIT Block

Lecture – 1

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

Microbiology Team - 430

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Definition of Peptic Ulcer Disease (PUD):

- It is an ulcer defined as mucosal erosions (≥ 0.5cm) that is created in an acidic area. There are more Peptic ulcers arising from duodenum than stomach.
  - ➢ 4% of stomach ulcer can turn to be malignant tumor on the other hand Duodenal ulcers are generally benign.
  - ➢ Multiple biopsies are needed to exclude cancer.

Signs and symptoms:

- Abdominal pain, epigastric with severity relating to meal time (3 hr after meal with gastric ulcer, but in case of duodenal ulcer the pain is not associate with meal).
- Bloating & abdominal fullness.
- Nausea and vomiting associated with loss of appetite and weight loss.
- Haematemesis (vomiting of blood) due to gastric or esophagus damage.
- Melena (foul-smelling faeces due to oxidized hemoglobin iron).
  - ✓ Rarely; Gastric or duodenal perforation leading to acute peritonitis (extremely painful-requires urgent surgery).

Old-management:

- They used to open the abdomen, sewing up to the hole and avoiding inflammation with cleansing abdomen cavity.
- Peptic ulcer was a dangerous disease associated with high morbidity and mortality.
- Nowadays gastrectomy (where part of the stomach or all is resected), is no longer used for peptic ulcer management. (only in case of cancer)

Helicobacter pylori:

- Helicobacter pylori (formerly known as Campylobacter.pylori or C.pyloridis) are 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.
- 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.
- It is most likely to be found in the pyloric part of the stomach near the pyloric sphincter (the circular opening leading from the stomach into the duodenum) and then cause duodenal ulcer.

Laboratory characteristics:

Morphology & staining	Culture	Biochemical reactions	Typing	Serology
• Small, Gram-negative, spiral rods, motile by polar flagella.	• On blood or chocolate agar in a moist microaerophilic atmosphere.(O_2 concentration is lower than found in the air) • For isolation from clinical specimens, use campylobacter selective medium. Small colonies grow after 3-7 days at 37˚C.	• Catalase-positive • oxidase-positive • Strongly urease-positive.	• No agreed typing scheme .	• IgG and IgM to Cytotoxic • Associated Gene A (CagA) and (VacA) for virulence strains. (*CagA→ associated with converting ulcer into malignant. * VacA→ associated with formation the ulcer)

Diagnosis:

- Checking dyspeptic patients for H pylori. (patients with stomach upset or indigestion)
- **Non-invasive methods:**
  1. Blood antibody test (IgG, IgM or IgA).
  2. Stool antigen test.
  3. Carbon urea breath test (C^{14} or C^{13}).

When they demonstrate the immune reaction to the stomach infection

Patients swallow urea labeled with either C^{14} or C^{13} and →urea breakdown in the stomach and release CO_2 → detect the percentage of CO_2 that comes out from the mouth → if it is 60% or 70% → confirm diagnosis.

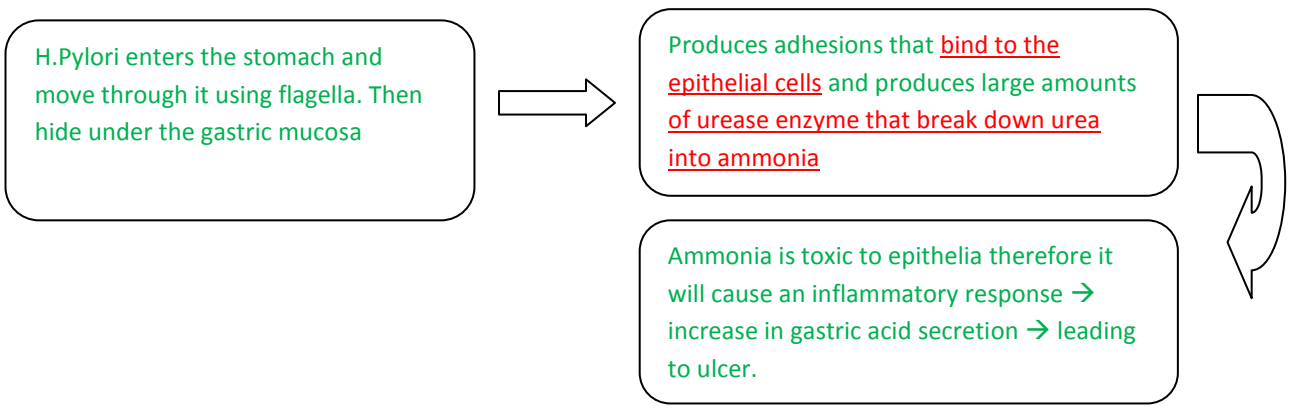
- **Invasive methods (most reliable):**
  1. Endoscopy followed by Histological examination.
  2. Endoscopy followed by culturing the bacteria.

Genome:

- Study of H pylori is centered on trying to understand the pathogenesis of genome database.
- H pylori consist of large diversity of strains with 1.550 genes and contain 40kb-long Cag pathogenicity island (PAI) with over 40 pathogenetic genes.
- The ***CagA* gene** codes on of the major *H pylori* **virulence** proteins.
- **Asymptomatic** patients carry *H pylori* strains lacking the Cag pathogenicity island (PAI). (we should not kill the organism otherwise , other virulent organisms will colonize in the stomach and cause problems)

Pathophysiology:

- To colonize the stomach, H pylori must survive acidity. Therefore it uses flagella to move through stomach lumen and drill into the mucoid lining of stomach (hide)
- Produces adhesions that **bind to the epithelial cells** and produces large amounts **of urease enzyme that break down urea into** co2 +**ammonia**. This in-turn neutralizes gastric acid. (the neutralization is only around the bacteria → meaning it does not overcome the acidity)
- **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 stimulates 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 pylorus induces the production of **TNF-α** and **Interleukin 6 & 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 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. (Most effected method).**
  - ✓ So there is no useful vaccine

Epidemiology:

- Around 50% of world's population harbor H pylori. 3rd world has more rate of infection and the 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. (any regimen should involve these 2 antibiotics because it has been proved that they are the best although H.Pylori becoming resistant in some developing countries and in order to overcome these resistant we start using a combination of multiple antibiotics)
- **Transmission:**
  - **Contagious** with an unknown route of transmission
  - **Person to person** (oral to oral or fecal-oral) route.
  - 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 (outside the body):** H.pylori is sensitive to amoxicillin, tetracycline, metronidazole, Macrolides (clarithromycin).
- **In vivo (inside the body):** 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. (So, the antibiotic must has the ability to overcome gastric acidity)
- Recently, Metronidazole in developing countries is becoming resistance (80-90%).

Triple therapies:

- **One-week combination**:
  - Omeprazole + Clarithromycin + Tinidazole. Rate of eradication was 95%-100%.
- **10 days combination**:
  - Ranitidine Bismuth citrate + Amoxicillin + Clarithromycin with an eradication rate of no more than 75%.
- **10 days combination:**
  - Ranitidine Bismuth citrate + Clarithromycin + Metronidazole with an eradication rate of 90%.
- **One-week combination:**
  - Omeprazole + Amoxicillin + Metronidazole the rate of eradication was 96 % (very cost effective)

Quadruple Therapies:

- 7 days regimen of combination of Omeprazole, Amoxicillin, metronidazole and proton pump inhibitor (PPI) has 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 Pseudo membranous colitis in 11% of patients.

Summary

- When abdominal pain is associate with meals its properly gastric ulcer. If not it most likely to be a case of duodenal ulcer
- Peptic ulcer is characterized by an **abdominal pain, Melena**, bloating and **Haematemesis**
- H.Pylori are found closely associated with gastric mucosa and causes **chronic active gastritis**, gastric and duodenal ulcer (**Peptic ulcer**) & **adenocarcinoma**
- H.Pylori is a gram –ve bacteria that can grow on **campylobacter selective medium. Small colonies after 3-7 days.**
- Diagnosis of infection is usually made by checking for dyspeptic symptoms and some other tests. However, **the most reliable method for detecting H. pylori** infection **is endoscopy** followed by histological examination and microbial culture. We can also use **Carbon urea breath test** (C^{14} or C^{13})
- Bacterial strains that have the **CagA gene** are associated with an ability to **cause ulcers** .Therefore; patients carry H pylori strains lacking the Cag pathogenicity island (PAI) are **Asymptomatic**
- H.Pylori enters the stomach and move through it using flagella. Then hide under the gastric mucosa. Produces adhesions that **bind to the epithelial cells** and **produces large amounts of urease enzyme that break down urea into ammonia** which is toxic to epithelia therefore it will cause an inflammatory response which lead into ulcer
- **Proper sanitation and clean sources of drinking water** is the most effective way to **prevent** H.Pylori infection
- The standard first-line therapy is a one week "triple therapy" consisting of proton pump inhibitors (such as omeprazole, lansoprazole) and antibiotics
- The most effective thereby and the one that it used in KSA is : **One-week combination of Omeprazole + Amoxicillin + Metronidazole**
- Recently, antibiotics (metronidazole, clarithromycin) are becoming resistance to H pylori.