Case scenario

L1&2: Gastroesophageal Reflux Disease & Peptic Ulcer

objectives

- Describe the definition, pathogenesis, clinical features, pathology (gross and microscopic features) and complications of reflux esophagitis.
- Describe the definition, main cause, pathology (gross and microscopic features) and complications (dysplasia and adenocarcinoma) of Barrett esophagus.
- Define ulcer and erosion.
- Describe the pathogenesis, pathology and clinical features of acute gastric ulcers.
- Describe the pathogenesis (H pylori, NSAID, Z-E syndrome), clinical features, pathology (gross and microscopic features) and complications (bleeding, perforation, obstruction) of chronic peptic ulcers.

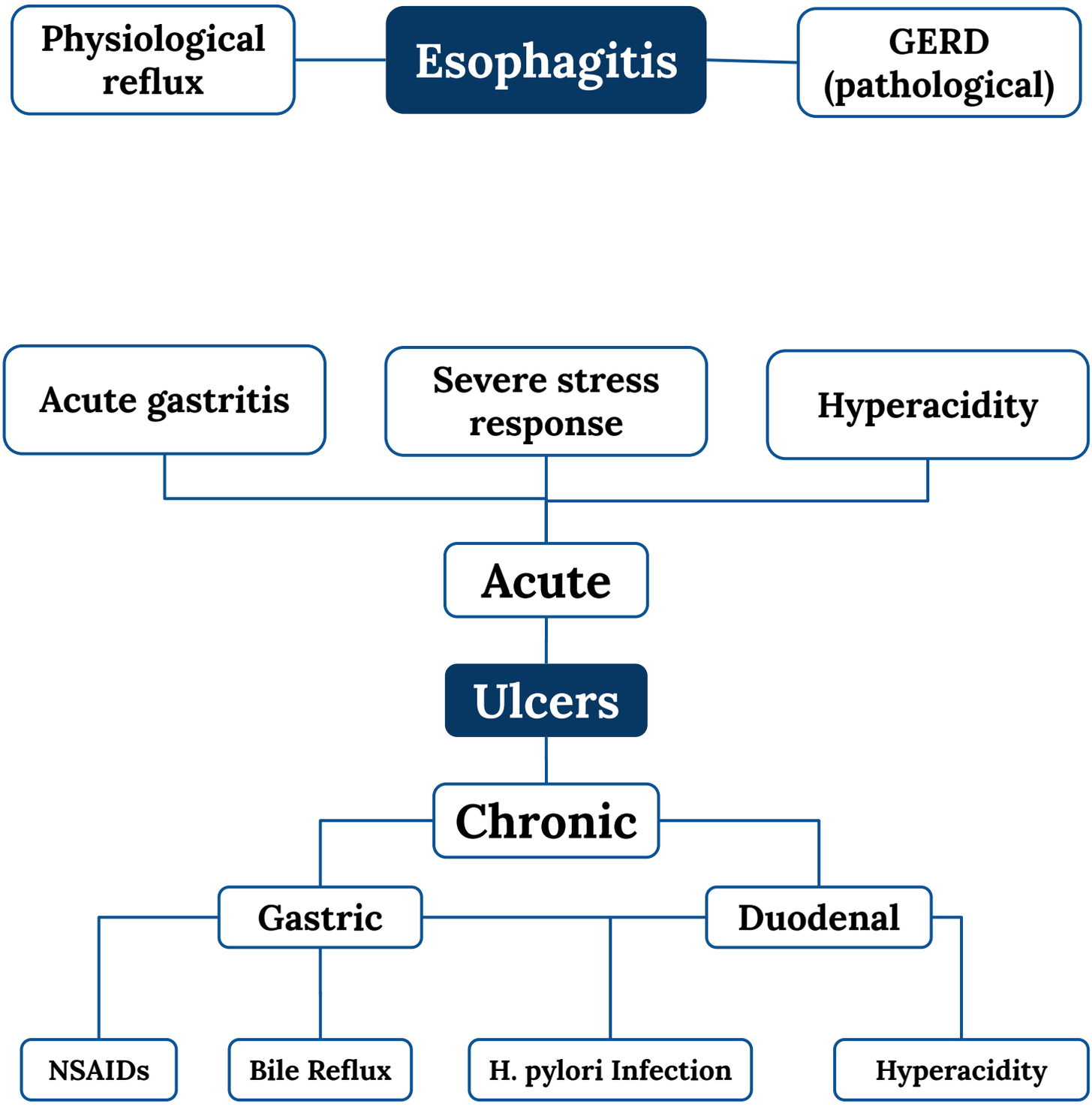
Black: original content
Red: Important
Green: only found in males slides

Orange: Doctor notes
Grey: Extra/Robbins
Purple: Only found in females slides

Reviewed by: Razan AlRabah & Ibrahim AlDakhil

Editing File

Lecture Content



Esophagitis

Reflux esophagitis

- Symptoms or mucosal damage produced by the abnormal reflux of gastric content into the esophagus, often chronic and relapsing.
- Esophagitis is **rarely caused by anything other than reflux**.
- May see complications of GERD in patients who lack typical symptoms.
- Some other causes include:
  - **Infective**
    - Fungal infection (common): candida albicans.
    - Viral infection: **Herpes simplex** and **cytomegalovirus** in **AIDS** patients.
    - Bacterial infection is very rare.
  - **Physical Agent**
    - Irradiation
    - Ingestion of caustic agent

Gastroesophageal reflux	Gastroesophageal reflux disease (GERD)
A **normal physiological** phenomena experienced intermittently by most people: • **After a meal (postprandial)** • Short lived • Asymptomatic • No nocturnal symptoms	The amount of gastric juice that refluxes into the the esophagus **exceeds the normal limit**, causing: • **Symptoms** • with or without **esophageal mucosal injury** • **Nocturnal symptoms**

Epidemiology of GERD

- 44% of americans have heartburns at least once a month (physiological type).
- 14% have weekly symptoms (GERD).
- 7% have daily symptoms (GERD).
- 80% of pregnant women have GERD.
- Hiatal hernia is present in 70% of people with GERD.

Symptoms

- **Typical:**
  - **Heartburning**; retrosternal burning.
  - **Regurgitation**; (feeling of acidity in throat) effortless return of gastric content into the pharynx, without nausea, retching, or abdominal contractions.
- **Atypical (**usually in older age group**)**:
  - Coughing: At night or during sleep
  - Chest pain: similar to Angina
  - Wheezing: Fluid return to pharynx → larynx → irritation → bronchospasm

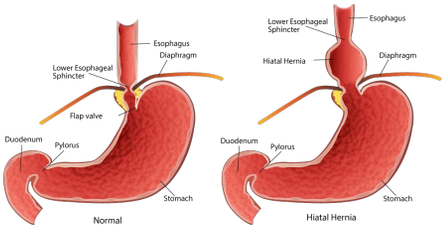
GERD

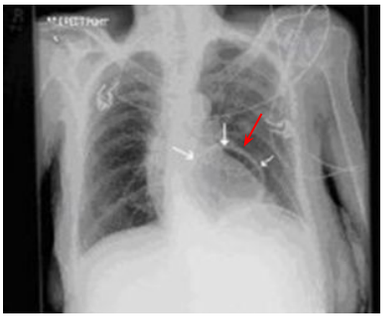
Pathophysiology

Abnormal Lower esophageal sphincter (LES)	Increased abdominal pressure
The LES prevents the gastric juice from reaching the esophagus, which is sensitive to its acidity. 1. **Functional**; frequent transient LES relaxation 2. **Mechanical**; hypotensive LES 3. **Food**; coffee, alcohol, smoking 4. **Medication;** calcium channel blocker, CNS depressants. 5. **Location: hiatal hernia** (X-ray show gas behind heart)	Increased pressure in the stomach compared to that of the esophagus allows for gastric content to reflux into the esophagus. 1. **Obesity** 2. **Pregnancy** 3. **Increased gastric volume after heavy meal.**

Risk Factors

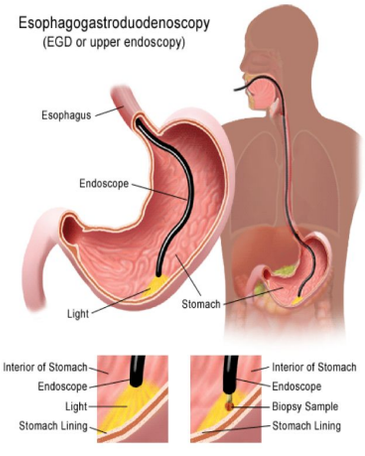
- Smoking, Alcohol.
- Caffeine, fatty foods, chocolate.
- Pregnancy, obesity.
- **Hiatal hernia:** Herniation of a portion of the stomach into the lower thorax.
  Types of hiatal hernia: Sliding (more common in GERD) and rolling.





Diagnosis

- If typical symptoms are present, without atypical symptoms, diagnosis is made clinically without further evaluation.
- **Endoscopy (**with biopsy if needed) is done rarely:
  - Patients with alarm symptoms; dysphagia, which indicated there is complications.
  - Patients who fail medication trial.
  - Those who require long-term treatment.
- **24-hour pH monitoring:**
  - For establishing and excluding GERD, for patients who do not have mucosal change.

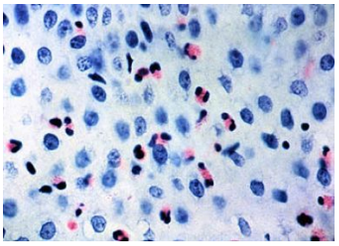


GERD

Complications

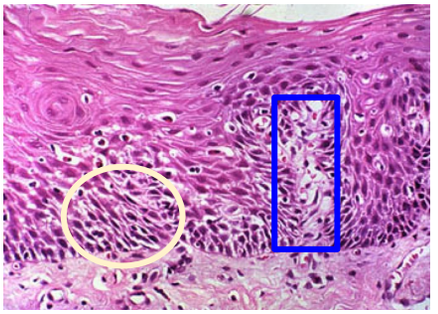
1- Hematemesis: the vomiting of blood.

2- Melena: black tarry stools.



3- Erosive esophagitis

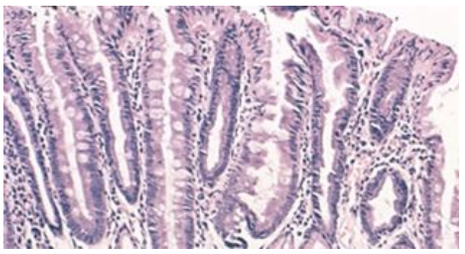
- Responsible for 40-60% of GERD symptoms.
- Severity of symptoms might not match severity of esophagitis.
- **Morphology:**
  - Basal zone hyperplasia.
  - Elongation of lamina propria.
  - Eosinophils and neutrophils.
  - Red mucosa with erosions and ulceration.



4- Esophageal stricture

- Narrowing of esophagus, due to healing erosive esophagitis.
- May need dilation.

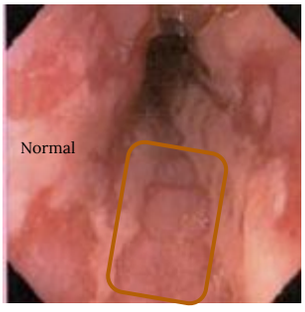
5- Barrett's esophagus



- Intestinal metaplasia of the esophagus. The stratified squamous epithelium of the esophagus becomes columnar with goblet cells, in the lower esophagus.
- Patients may be asymptomatic.
- The incidence of Barrett esophagus is rising.
- Occur in 10% of individuals with symptomatic GERD.
- Most common in white males and typically presents between 40 and 60 years.
- Can only be identified through endoscopy and biopsy, due to GERD symptoms.
- **Pathophysiology:**

Reflux acid damages the lining of the esophagus causing chronic esophagitis → Healing in a metaplastic process results in columnar cells replacing squamous cells → Could progress to dysplasia and adenocarcinoma

Short segments



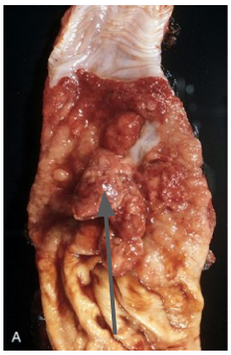
Endoscopic image of barrett's esophagus: an area of red mucosa
Long segments, tongue like processes + dysplasia

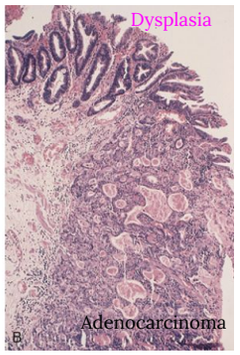
Long segments, Irregular and rough processes

Mass → adenocarcinoma

GERD

- **Complications of Barrett's esophagus:**





Adenocarcinoma

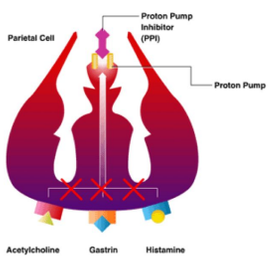
  - **Dysplasia**
    - The presence of dysplasia, a preinvasive change, is associated with prolonged symptoms, longer segment length, increased patient age, and Caucasian race.
    - **Low-grade dysplasia:** Cytological changes e.g. nuclear stratification, hyperchromasia and increased nuclear to cytoplasmic ratio.
    - **High-grade dysplasia:** Architectural irregularities, including gland within gland, or cribriform pattern in addition to cytological changes.
  - **Adenocarcinoma**
    - Risk factors other than Barrett's esophagus: tobacco and radiation.
    - The risk is reduced by diets rich in fresh fruits and vegetables.
    - Occurs in the distal third of the esophagus and may invade the adjacent gastric cardia.
    - Well to poorly differentiated adenocarcinoma.
    - Present with pain or difficulty in swallowing, progressive weight loss, hematemesis, chest pain, or vomiting.
    - Prognosis depends on the stage.

6- Squamous carcinoma

- Most common in middle and lower esophagus.
- Common in men who are heavy smokers or alcohol drinkers.
- Maybe preceded by epithelial dysplasia.
- The most common malignant tumors of the esophagus are squamous carcinoma and adenocarcinoma. Both have poor prognosis.
- Not related to GERD 

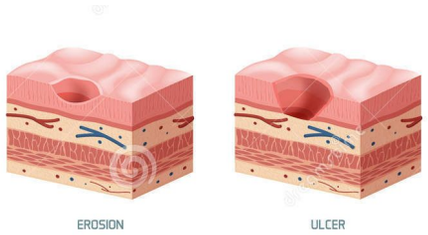
Treatment

- **H2** receptor blockers
- Proton pump inhibitor
- May require antireflux surgery



Ulcers

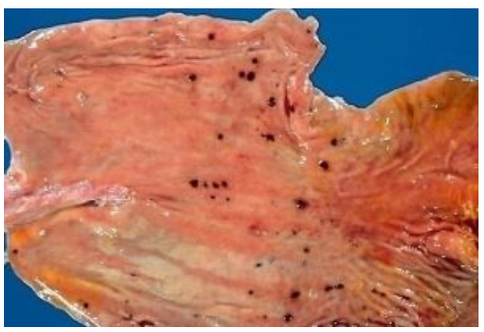
- **Erosion:** is a breach in the epithelium of the mucosa only.
- **Ulcer:** is a breach in the mucosa of the alimentary tract extending through muscularis mucosa **into submucosa** or deeper.
  - **Types:**
    i. **Peptic ulcer:** chronic.
    ii. **Stress ulcers:** acute gastric (peptic) ulcers.
  - **Pathophysiology:** imbalance between aggressive factors & defensive factors:



Aggressive Factors	Defensive Factors
H. pylori	Mucus
Drugs (NSAIDs)	bicarbonate
Acid	Blood flow & Cell renewal
pepsin	Prostaglandins
Bile salts	Phospholipid

Acute peptic ulcers (stress ulcers)

- **Pathophysiology:**
  - Part of an acute gastritis:
    - Acute response to an irritant 'chemical' injury by drugs:
      - NSAIDs
      - Alcohol
  - Complication of a severe stress response:
    - Severe burns (Curling's ulcer)
    - Major trauma (Cushing ulcer)
    - Cerebrovascular accidents (Cushing ulcer)
  - A result of extreme hyperacidity:
    - Zollinger-Ellison syndrome[1]

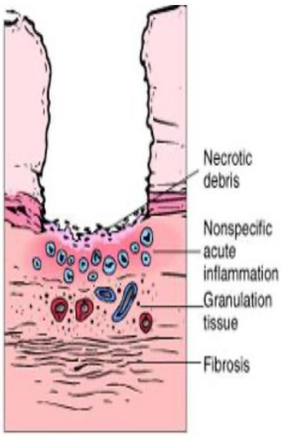


Location	Morphology	Prognosis	Clinical findings:
Anywhere in the stomach	They range in depth from very superficial lesions (**erosion**) to deeper lesions that involve the entire mucosal thickness (**true ulceration**)	The gastric mucosa can recover completely if the person does not die from the primary disease	a. Hematemesis b. Melena c. Iron deficiency due to chronic bleeding.

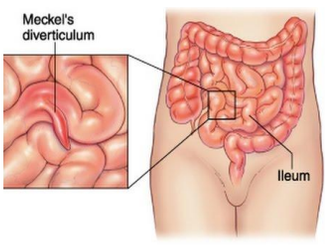
1. A condition in which a gastrin-secreting tumour or hyperplasia of the islet cells in the pancreas causes overproduction of gastric acid, resulting in recurrent peptic ulcers.

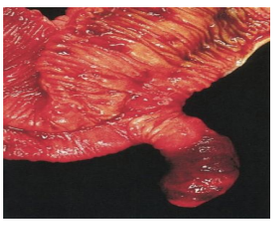
Ulcers

Peptic Ulcer Disease (Chronic peptic ulcer)



- Peptic ulcers are chronic, recurring lesions that occur most often in middle-aged to older adults without obvious precipitating conditions, other than chronic gastritis.
- **Locations**
  - May occur anywhere, often solitary in GI tract exposed to **acidic gastric juices.**
  - 98% located in first portion of **duodenum** or **stomach** (Ratio =4:1)
    - Gastric peptic ulcers are predominantly located near the interface of the body and antrum at lesser curvature.
    - Duodenal ulcers usually occur within a few centimeters of the pyloric valve at the anterior duodenal wall.
  - Esophagus, as a result of **GERD** or acid secretion by ectopic gastric mucosa.
  - Gastric mucosa within a ***Meckel diverticulum*** can result in peptic ulceration of adjacent mucosa.
    - Most common congenital abnormality of the small intestine caused by an incomplete obliteration of the vitelline duct,
      Simply it's normal tissue at abnormal location, so if Gastric tissue is in the small intestine it will cause peptic ulceration of of adjacent mucosa. (More info)
  - In **Zollinger-Ellison syndrome:** multiple peptic ulcerations in the stomach, duodenum, and even the jejunum.





- **Mucosal defences** against acid attack consist of:

1) Mucus-bicarbonate barrier		2) Surface epithelium
Disrupted by	**Duodeno-gastric reflux** (bile)	**NSAIDs** (blocking the synthesis of the prostaglandins)
		H. pylori infection[1] (cytotoxins and ammonia)

- **Note:**
  1. Helicobacter Pylori **does not** colonise normal duodenal epithelium. If it undergoes ***Gastric metaplasia*** in response to excess acid damage it will pave the way for colonisation by Helicobacter.

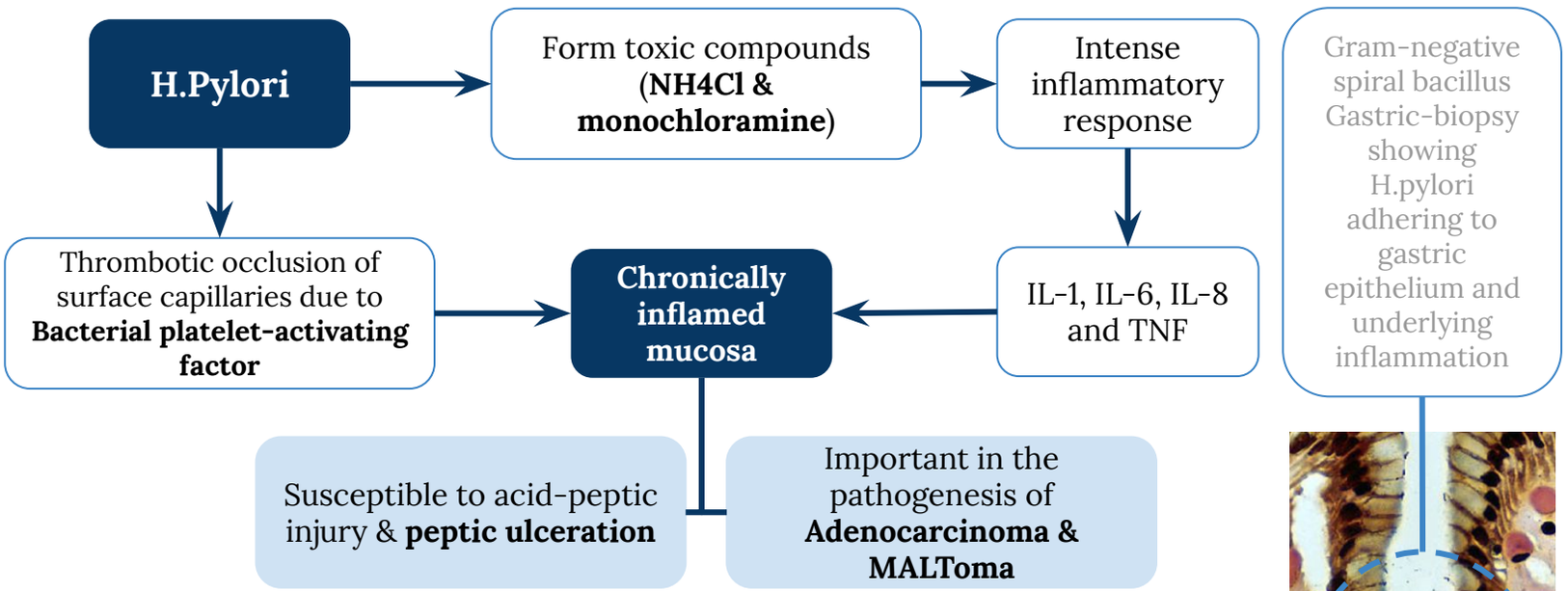
Ulcers

Peptic Ulcer Disease (Chronic peptic ulcer) Cont.

	Duodenal Ulcer	Gastric Ulcer
Most important factor	**Increased Acid production** Hyperacidity	**Breakdown of mucosal defence** Nsaids & Duodeno-gastric reflux (bile)
H pylori infection of the pyloric antrum	Almost all patients	Approximately 75% of patients

- **H. pylori** infected individuals secrete **2-6 times** as much acid as non-infected controls (hyperacidity).
- **Only 20% of H. pylori–infected individuals develop peptic ulcer.**

- **Pathogenesis:**

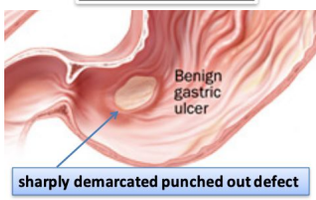


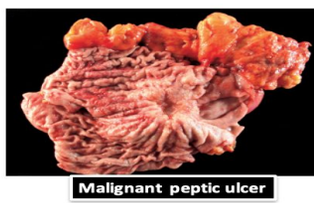
- **H. pylori Virulence factors**:
  - VacA (direct cell injury).
  - CagA promotes inflammation & tissue damage.
  - Flagella (motility).
  - Bacterial Adhesions.
  - Urease that breaks down urea to make ammonia.
  - Lipopolysaccharides, recruit inflammatory cells to the mucosa.

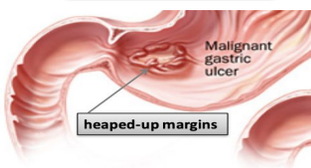
- **Other causes:**
  - NSAID and aspirin.
  - High-dose corticosteroids, which suppress prostaglandin synthesis.
  - Cigarette smoking: impairs mucosal blood flow and healing.
  - **Chronic renal failure**, and **hyperparathyroidism** associated with hypercalcemia, stimulate gastrin production and therefore increase acid secretion.
  - Psychological stress (can increase gastric acid secretion).

Ulcers

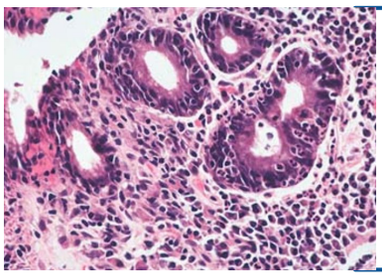
Peptic Ulcer Disease (Chronic peptic ulcer) Con..



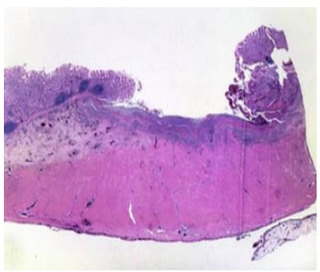




- **Morphology**
  - **Gross:**
    - Usually <20 mm in diameter but they may > 100 mm in diameter.
    - The classic peptic ulcer is a round to oval, **sharply punched-out defect,** with straight walls, surrounded by hyperemia.
    - In contrast, **heaped-up margins** are more characteristic of **cancers.**
    - Most gastric ulcers are benign. A small percentage may be malignant, (reason for biopsy)
    - Duodenal ulcers are never malignant (reason for not taking a biopsy)
  - **Microscopy:**
    - Base consists of necrotic tissue and polymorph exudate overlying inflamed granulation tissue which merges with mature fibrous (scar) tissue.



The presence of neutrophils within the gastric glands signifies active inflammation and, most of the time, the presence of H pylori.



- **Clinical features**
  - **Epigastric pain,** the most common symptom:
    - Gnawing or burning sensation

Duodenal Ulcer	Gastric Ulcer
Food relieves pain	Food aggravates pain
Epigastric pain 2-3 hours after meal	Epigastric pain shortly after meal
Vomiting not common	Vomiting Is common
Patient awakens with pain at night.	Rarely occurs at night

- **Complications** of Chronic Peptic Ulcers:
  - Iron deficiency anemia and Hemorrhage (frank hemorrhage).
  - Penetration The ulcer penetrates the full thickness of the stomach or duodenal wall, progressing into adherent underlying tissue, e.g. the pancreas or liver.
  - Perforation leading to peritonitis, Fibrous stricture causing pyloric stenosis, Malignant change (uncommon).

- **Therapy**
  - H. pylori eradication: Antibiotics.
  - Acid suppression: Proton pump inhibitors and H2 blockers.

Summary (Ulcers)

Pathophysiology and etiology of acute and chronic peptic ulcer

imbalance

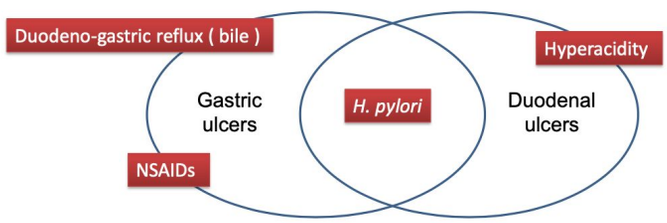
↑ Aggressive Factors	Defensive Factors ↓
H. pylori	Mucus
Drugs (NSAIDs)	bicarbonate
Acid	Blood flow & Cell renewal
pepsin	Prostaglandins
Bile salts	Phospholipid

Acute Ulcers Etiology

- Acute gastritis
- Severe stress response
- Extreme hyperacidity

Chronic Ulcers

Gastric	Duodenal
H. pylori Infection	H. pylori Infection
NSAIDs	Hyperacidity
Bile Reflux	
Worsen by food	**Relieved by food**
Malignant associated	**Not Malignant associated**



Clinical features of Acute and chronic Peptic Ulcer

- Epigastric pain
- Nausea & vomiting
- Loss of appetite

Quiz

Q1: A 45-year-old man presents with long-standing heartburn and dyspepsia. An X-ray film of the chest shows a retrocardiac, gas-filled structure. This patient most likely has which of the following conditions?

A) Esophageal varices
B) Esophageal webs
C) Hiatal hernia
D) Mallory-Weiss syndrome

Q2: A 57-year-old woman has had burning epigastric pain after meals for more than 1 year. Upper gastrointestinal endoscopy shows an erythematous patch in the lower esophageal mucosa. A biopsy specimen shows basal zone squamous epithelial hyperplasia, elongation of lamina propria papillae, and scattered intraepithelial neutrophils with some eosinophils. Which of the following is the most likely diagnosis?

A) Barrett's esophagus
B) Esophageal varices
C) Iron deficiency
D) Reflux esophagitis

Q3: Which of the following is a typical symptom of GERD

A) coughing
B) wheezing
C) Retrosternal burning sensation
D) Nocturnal angina

Q4: A 50-year-old obese man (BMI = 32 kg/m2) comes to the physician complaining of indigestion after meals, bloating, and heartburn. Vital signs are normal. A CT scan of the abdomen reveals a hiatal hernia of the esophagus. Endoscopic biopsy shows thickening of the basal layer of the squamous epithelium, upward extension of the papillae of the lamina propria, and an increased number of neutrophils and lymphocytes. Which of the following is the most likely diagnosis?

A) Esophageal varices
B) Schatzki mucosal ring
C) Squamous cell carcinoma
D) Reflux esophagitis

Q5: A 68-year-old man from Birmingham, England, has had "heartburn" and substernal pain after meals for 25 years. For the past year, he has had increased pain with difficulty swallowing both liquids and solids. On physical examination, there are no remarkable findings. Upper gastrointestinal endoscopy shows an ulcerated lower esophageal mass that nearly occludes the lumen of the esophagus. A biopsy specimen of this mass is most likely to show which of the following neoplasms?

A) Squamous cell carcinoma
B) Barrett's esophagus
C) adenocarcinoma
D) leiomyosarcoma

1-C
2-D
3-C
4-D
5-C

Quiz

Q1: Which of the following is a defensive factor for peptic ulcer?

A) Prostaglandins
B) pepsin
C) Bile salts
D) Acidity

Q2: Acute peptic ulcer can be caused by Extreme hyperacidity, which of the following can cause that?

A) Major trauma
B) Severe burns
C) Zollinger-Ellison syndrome
D) CVA

Q3: which of the following is the most common site of Chronic peptic Ulcers?

A) Soft palate
B) Stomach
C) Esophagus
D) Duodenum

Q4: Which of the following can most likely disrupt the Mucus-bicarbonate barrier ?

A) Duodeno-gastric reflux
B) NSAIDs
C) H. pylori infection
D) Ammonia

Q5: Normally H.pylori can not colonize the small intestine, But what can make the duodenum suitable to be colonized by H.pylori?

A) Gastric metaplasia
B) Decrease mucus secretion
C) Decreased Motility of small intestine
D) Hyperplasia

Q6: which of the following is a character of almost all duodenal ulcer patients?

A) Blood group A
B) H pylori infected
C) Fever
D) Female

Q7: which of the following tumors can arise from a peptic ulcer?

A) Adenocarcinoma
B) MALToma
C) Meningioma
D) A&B

Q8: which of the following is a Virulence factors for H.pylori?

A) Serine proteases
B) Alpha-toxin
C) M protein
D) CagA

Q9: which of the following is a gross characteristic of benign peptic ulcer

A) Heaped-up margins
B) Sharply punched-out defect
C) Poorly demarcated
D) Multiple Ulcers

1-A 2-C 3-D 4-A 5-A 6-B 7-D 8-D 9-B

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THANK YOU