Peptic Ulcer Disease

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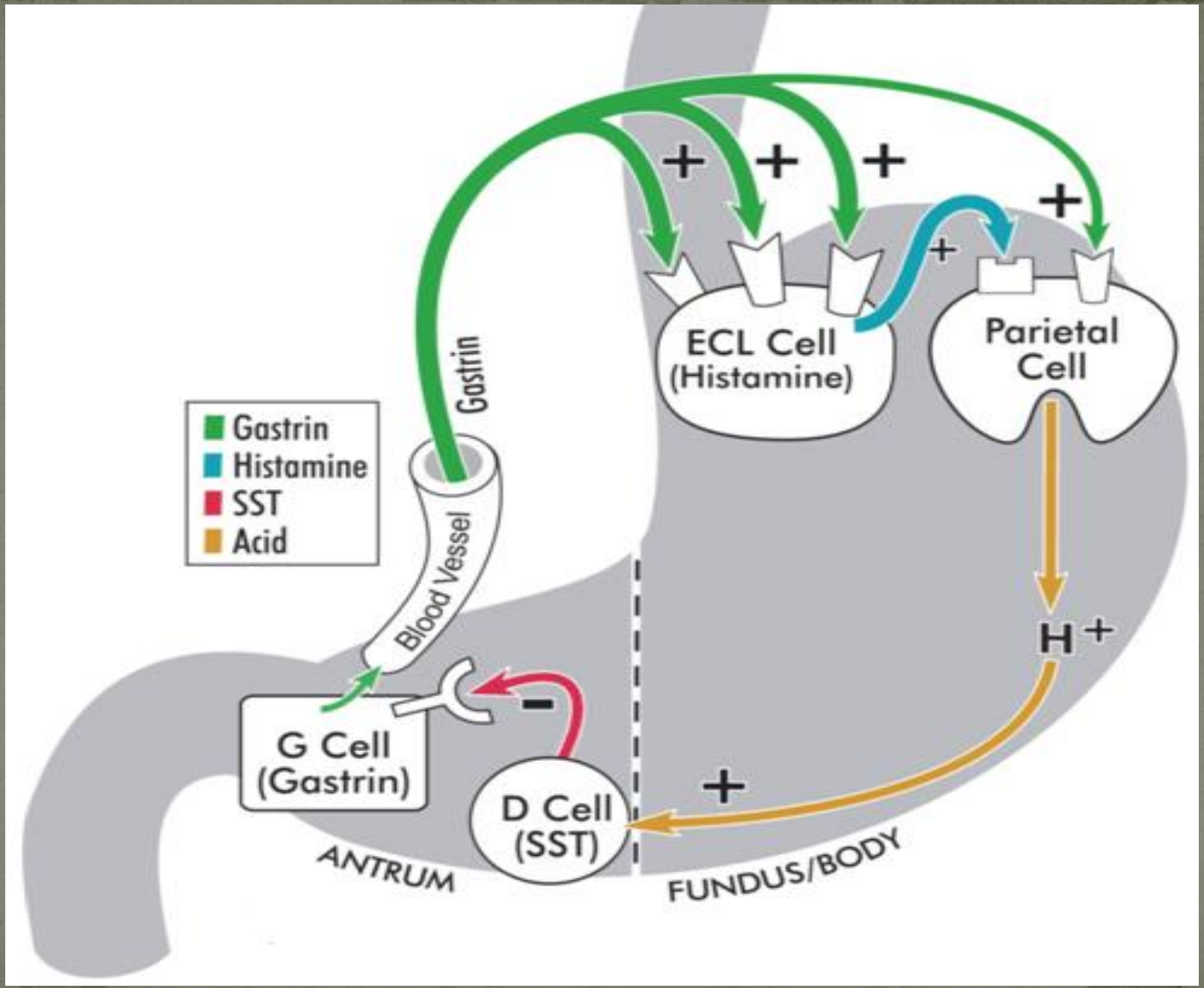
The Stomach

- The antral mucosa secretes bicarbonate and contains mucus-secreting cells and G cells, which secrete gastrin
- Somatostatin is also produced by specialized antral cells (D cells)
- Mucus-secreting cells are present throughout the stomach and secrete mucus and bicarbonate
- The 'mucosal barrier', made up of the plasma membranes of mucosal cells and the mucus layer, protects the gastric epithelium from damage by acid
- Prostaglandins stimulate secretion of mucus, and their synthesis is inhibited by inhibition of cyclo-oxygenase

The Stomach

- The duodenal mucosa has villi like the rest of the small bowel, and also contains Brunner's glands that secrete alkaline mucus. This, along with the pancreatic and biliary secretions, helps to neutralize the acid secretion from the stomach
- Acid secretion is under neural and hormonal control. Both stimulate acid secretion through the direct action of histamine on the parietal cell
- Acetylcholine and gastrin also release histamine via the enterochromaffin cells (ECL)
- Somatostatin inhibits both histamine and gastrin release and therefore acid secretion


Gastrin
Histamine
SST
Acid
Gastrin
Blood Vessel
ECL Cell
(Histamine)
Parietal
Cell
H+
G Cell
(Gastrin)
D Cell
(SST)
ANTRUM
FUNDUS/BODY

The Stomach

- Acid itself is not essential for digestion but does prevent some food-borne infections

- Other major gastric functions are:
  - reservoir for food
  - emulsification of fat and mixing of gastric contents
  - secretion of intrinsic factor
  - absorption (of only minimal importance)

Epidemiology of peptic ulcer disease

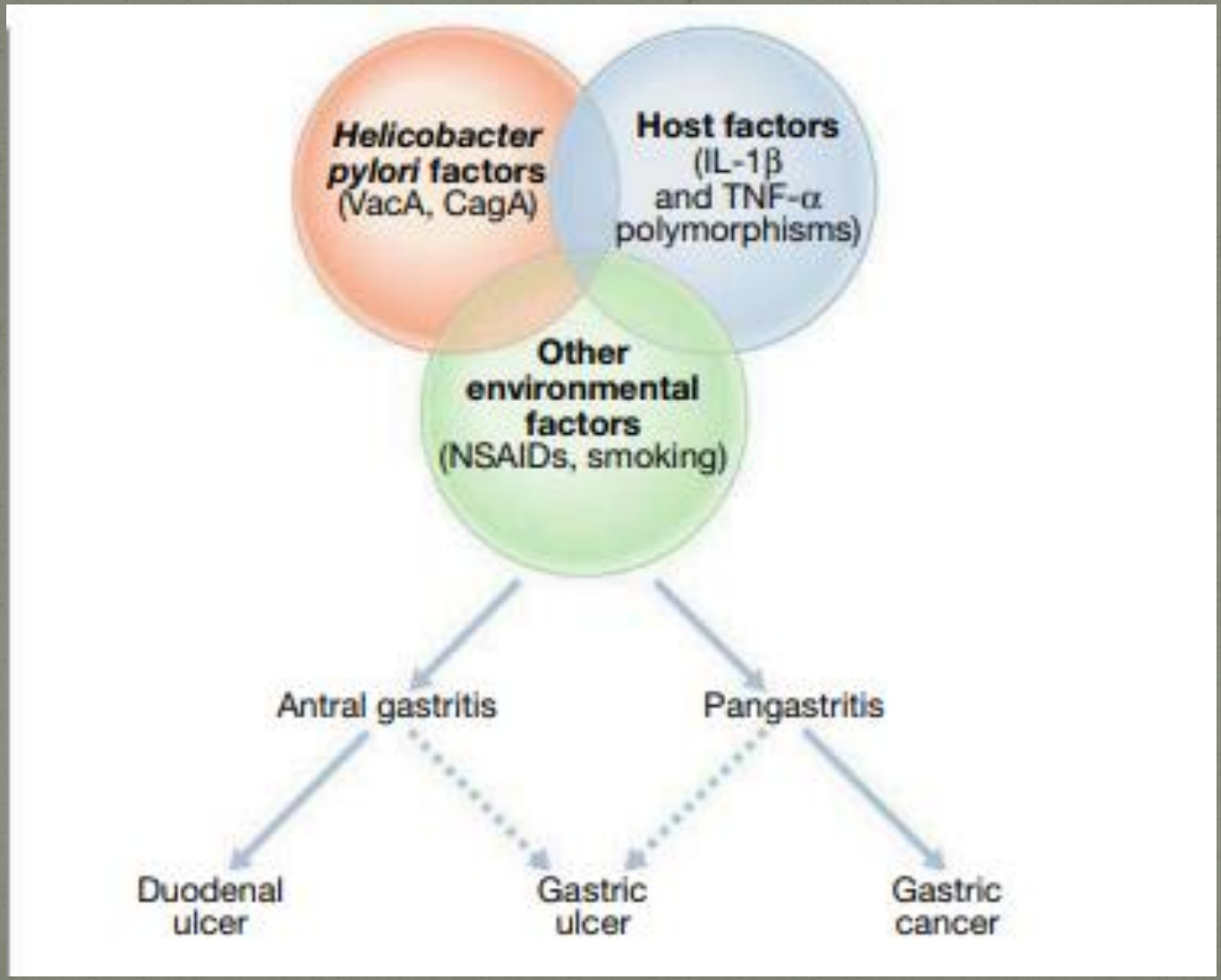
- The lifetime prevalence of peptic ulcer is around 5%–10%. The incidence is decreasing
- The male-to-female ratio for duodenal ulcer varies from 5:1 to 2:1, while that for gastric ulcer is 2:1 or less.
- Both DUs and GUs are common in the elderly
- There is considerable geographical variation, with peptic ulcer disease being more prevalent in developing countries related to the high H. pylori infection
- Around 90% of duodenal ulcer patients and 70% of gastric ulcer patients are infected with H. pylori

Pathology of peptic ulcer disease

- A peptic ulcer consists of a break in the superficial epithelial cells penetrating down to the muscularis mucosa; there is a fibrous base and an increase in inflammatory cells
- Erosions, by contrast, are superficial breaks in the mucosa alone
- The surrounding mucosa appears inflamed, hemorrhagic or friable
- GUs are most commonly seen on the lesser curve, but can be found in any part of the stomach.
- Peptic ulcers are seen without H. pylori, e.g. in patients on NSAIDs and in smokers

Helicobacter pylori infection

- H. pylori is Gram-negative and spiral, and has multiple flagella at one end, which make it motile, allowing it to burrow and live beneath the mucus layer adherent to the epithelial surface. Here the surface pH is close to neutral and any acidity is buffered by the organism's production of the enzyme urease.
- H. pylori is found in greatest numbers under the mucus layer in gastric pits, where it adheres specifically to gastric epithelial cells
- It is protected from gastric acid by the juxtamucosal mucus layer which traps bicarbonate secreted by antral cells, and ammonia produced by bacterial urease


Helicobacter pylori factors
(VacA, CagA)
Host factors
(IL-1β
and TNF-α
polymorphisms)
Other
environmental
factors
(NSAIDs, smoking)
Antral gastritis
Pangastritis
Duodenal
ulcer
Gastric
ulcer
Gastric
cancer

- The prevalence of H. pylori is high in developing countries (80–90% of the population), and much lower (20–50%) in developed countries
- Infection rates are highest in lower income groups.
- Infection is usually acquired in childhood; it may be fecal–oral or oral–oral
- Once acquired, the infection persists for life unless treated
- The incidence increases with age, probably due to acquisition in childhood when hygiene was poorer, and not due to infection in adult life which is probably far less than 1% per year in developed countries.

Causes of Gastritis

Acute gastritis (often erosive and haemorrhagic)

- Aspirin, NSAIDs
- *Helicobacter pylori* (initial infection)
- Alcohol
- Other drugs, e.g. iron preparations
- Severe physiological stress, e.g. burns, multi-organ failure, central nervous system trauma
- Bile reflux, e.g. following gastric surgery
- Viral infections, e.g. CMV, herpes simplex virus in HIV/AIDS (Ch. 14)

Chronic non-specific gastritis

- *H. pylori* infection
- Autoimmune (pernicious anaemia)
- Post-gastrectomy

Chronic 'specific' forms (rare)

- Infections, e.g. CMV, tuberculosis
- Gastrointestinal diseases, e.g. Crohn's disease
- Systemic diseases, e.g. sarcoidosis, graft-versus-host disease
- Idiopathic, e.g. granulomatous gastritis

Acute infection with H .pylori may cause a transient clinical illness characterized by nausea and abdominal pain that may last for several days and is associated with acute histologic gastritis with PMNs. After these symptoms resolve, the majority progress to chronic infection with chronic, diffuse mucosal inflammation (gastritis) characterized by PMNs and lymphocytes

Results of infection:

- Antral gastritis
- Peptic ulcers (duodenal and gastric)
- Gastric cancer

Antral gastritis

- The usual effect of H. pylori infection
- It is usually asymptomatic, although occasionally patients without ulcers claim relief of dyspeptic symptoms after Helicobacter eradication
- Antral gastritis causes hypergastrinemia due to gastrin release from antral G cells
- The subsequent increase in acid output is usually asymptomatic

Duodenal Ulcer

- H. pylori is causally associated with DU disease
- In patients with DU 95% are infected with H. pylori in the antrum (antral gastritis)
- In developed countries, the prevalence of H. pylori is rapidly declining. In the United States, the prevalence rises from less than 10% in non-immigrants under age 30 years to over 50% in those over age 60 years.
- The precise mechanism of duodenal ulceration is unclear, as only 15% of patients infected with H. pylori (50–60% of the adult population world-wide) develop duodenal ulcers
- Factors that have been implicated include:

1. Increased acid secretion because of increased parietal cell mass and increased gastrin secretion
2. Smoking impairing mucosal healing.
3. Virulence factors such as Vac A (vacuolating toxin) and CagA (cytotoxic-associated protein) as well as urease and adherence factors

4. Decreased inhibition of acid secretion; H. pylori-induced gastritis reduces somatostatin production in the antrum with loss of the negative feedback on gastrin secretion

5. Genetic susceptibility: duodenal ulcers are more common in patients who have blood group O

6. Duodenal bicarbonate secretion is decreased by H.pylori inflammation and the damage and repair leads to gastric metaplasia which H. pylori colonizes, causing local release of cytokines and further damage

Gastric Ulcer

- Gastric ulcers are associated with a gastritis affecting the body as well as the antrum of the stomach (pangastritis) causing parietal cell loss and reduced acid production
- The ulcers are thought to occur because of reduction of gastric mucosal resistance due to cytokine production by the infection or perhaps to alterations in gastric mucus

Clinical features of peptic ulcer disease

- The characteristic feature of peptic ulcer is burning epigastric pain
- The relationship of the pain to food is variable
- The pain of a DU classically occurs at night (as well as during the day) and is worse when the patient is hungry
- The pain of both gastric and duodenal ulcers may be relieved by antacids
- Nausea may accompany the pain; vomiting is infrequent but often relieves pain
- Anorexia and weight loss may occur, particularly with GUs

- Persistent and severe pain suggests complications such as penetration into other organs. Back pain suggests a penetrating posterior ulcer
- Severe ulceration can occasionally be symptomless, as many who present with acute ulcer bleeding or perforation have no preceding ulcer symptoms
- Untreated, the symptoms of a DU relapse and remit spontaneously
- The natural history is for the disease to remit over many years due to the onset of atrophic gastritis and a decrease in acid secretion
- Examination is usually unhelpful; epigastric tenderness is quite common in non-ulcer dyspepsia

Diagnosis of Helicobacter pylori infection

- Serological tests detect IgG antibodies and are reasonably sensitive (90%) and specific (83%)
- IgG titers may take up to 1 year to fall by 50% After eradication therapy and therefore are not useful for confirming eradication or the presence of a current infection.
- 13C-Urea breath test is a quick and reliable test for H. pylori and can be used as a screening test
- The measurement of $^{13}CO_2$ in the breath after ingestion of 13C urea requires a mass spectrometer
- The test is very sensitive (97%) and specific (96%)
- This test is suitable for testing for eradication of the organism, but may be falsely negative if patients are taking PPIs at the time

- Stool antigen test is a specific immunoassay using monoclonal antibodies for the qualitative detection of H. pylori antigen
- The overall sensitivity is 97.6% with a specificity of 96%. It is useful in the diagnosis of H. pylori infection and for monitoring efficacy of eradication therapy.
- Patients should be off PPIs for 1 week but can continue with H2 blockers

Invasive methods (Endoscopic)

- Biopsy urease test: Gastric biopsies are added to a substrate containing urea and phenol red. If H. pylori are present, the urease enzyme that they produce splits the urea to release ammonia which raises the pH of the solution and causes a rapid color change
- The test may be falsely negative if patients are taking PPIs or antibiotics at the time
- Culture: Biopsies obtained can be cultured on a special medium, and in vitro sensitivities to antibiotics can be tested.
- Histology: H. pylori can be detected histologically on routine stained sections of gastric mucosa

General Rules

- Patients under 50 years of age with typical symptoms of peptic ulcer disease who are H. pylori positive can start eradication therapy without investigation
- Confirmation of the diagnosis and exclusion of cancer is required in older patients
- Endoscopy is the preferred investigation. All GUs must be biopsied.
- Endoscopy is required in all patients with alarm symptoms:

1. dysphagia
2. weight loss
3. protracted vomiting
4. anorexia
5. hematemesis or melena
6. persistent symptoms

- Stopping smoking should be strongly encouraged as smoking slows mucosal healing
- Patients with gastric ulcers should be routinely reendoscoped at 6 weeks to exclude a malignant tumor

Eradication therapy

- All patients with duodenal and gastric ulcers should have H. pylori eradication therapy
- Eradication therapy is controversial in patients who have incidental H. pylori infection with no gastric or duodenal ulcer
- Standard eradication therapies are successful in approximately 90% of patients
- Reinfection is very uncommon (1%) in developed countries
- In developing countries reinfection is more common, as compliance with treatment may be poor and metronidazole resistance is high (> 50%)
- good compliance is essential
- oral metronidazole has frequent side-effects and bismuth chelate is unpleasant to take

- Metronidazole, clarithromycin, amoxicillin, tetracycline and bismuth are the most widely used agents
- Resistance to amoxicillin (1–2%) and tetracycline (< 1%) is low
- Quinolones such as ciprofloxacin, furazolidone and rifabutin are also used when standard regimens have failed 'rescue therapy'
- Bismuth suppresses H. pylori effectively
- None of these drugs is effective alone; eradication regimens therefore usually comprise two antibiotics given with powerful acid suppression in the form of a PPI, all given for 1-2 weeks
- Omeprazole 20 mg + clarithromycin 500 mg and amoxicillin 1 g – all twice daily
- Omeprazole 20 mg + metronidazole 400 mg and clarithromycin 500 mg – all twice daily

- In eradication failures bismuth chelate (120 mg 4× daily), metronidazole (400 mg 3× daily), tetracycline (500 mg 4× daily) and a PPI (20–40 mg 2× daily) for 14 days is used
- Sequential courses of therapy are being used in areas where resistance is high
- The effectiveness of treatment for uncomplicated duodenal ulcer should be assessed symptomatically
- If symptoms persist, breath or stool testing should be performed to check eradication
- Patients with a risk of bleeding or those with complications, i.e. hemorrhage or perforation, should always have a 13C urea breath test or stool test for H. pylori 6 weeks after the end of treatment to be sure eradication is successful
- Long-term PPIs may be necessary

Complications of peptic ulcer

- Hemorrhage
- Perforation: The frequency of perforation of peptic ulceration is decreasing, DUs perforate more commonly than GUs, usually into the peritoneal cavity. Surgery is usually performed to close the perforation and drain the abdomen
- Gastric outlet obstruction: The obstruction may be prepyloric, pyloric or duodenal. The obstruction occurs either because of an active ulcer with surrounding edema or because the healing of an ulcer has been followed by scarring.

Other *H. pylori*-associated diseases

- Gastric adenocarcinoma: The incidence of distal gastric cancer parallels that of H. pylori infection in countries with a high incidence of gastric cancer

- Gastric B cell lymphoma: Over 70% of patients with gastric B cell lymphomas (mucosal-associated lymphoid tissue – MALT) have H. pylori. Eradication cures this type of lymphoma

Thank You