Drugs Used in Peptic Ulcer

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Peptic Ulcer

- is a break in the lining of the stomach (**gastric ulcer**), first part of the small intestine (**duodenal ulcer**) or occasionally lower esophagus (**esophageal ulcer**).
- occur when the lining of these organs is corroded by the acidic digestive (peptic) juices which are secreted by the cells of the stomach.
- results probably due to an imbalance between the aggressive (acid, pepsin, bile and H. pylori) and the defensive (gastric mucus and bicarbonate secretion, prostaglandins) factors.

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Causes

- Helicobacter pylori
- NSAIDs
- Zollinger-Ellison Syndrome (Gastrinomas)
- Stress

Secretion of HCl by gastric parietal cell and its regulation

- The parietal cell contains receptors for gastrin, histamine (H2), and acetylcholine (muscarinic, M3).
- When acetylcholine or gastrin bind to the parietal cell receptors, they cause an increase in cytosolic calcium, which in tum stimulates protein kinases that stimulate acid secretion from a H+/K+ ATPase (the proton pump) on the canalicular surface.
- In close proximity to the parietal cells are gut endocrine cells called enterochromaffin-like (ECL) cells.
- ECL cells have receptors for gastrin and acetylcholine and are the major source for histamine release.

Regulation of gastric acid secretion

- Histamine binds to the H2 receptor on the parietal cell, resulting in activation of adenylyl cyclase, which increases intracellular cyclic adenosine monophosphate (cAMP).
- cAMP activates protein kinases that stimulate acid secretion by the H+/K+ ATPase.
- In humans, it is believed that the major effect of gastrin upon acid secretion is mediated indirectly through the release of histamine from ECL cells rather than through direct parietal cell stimulation.

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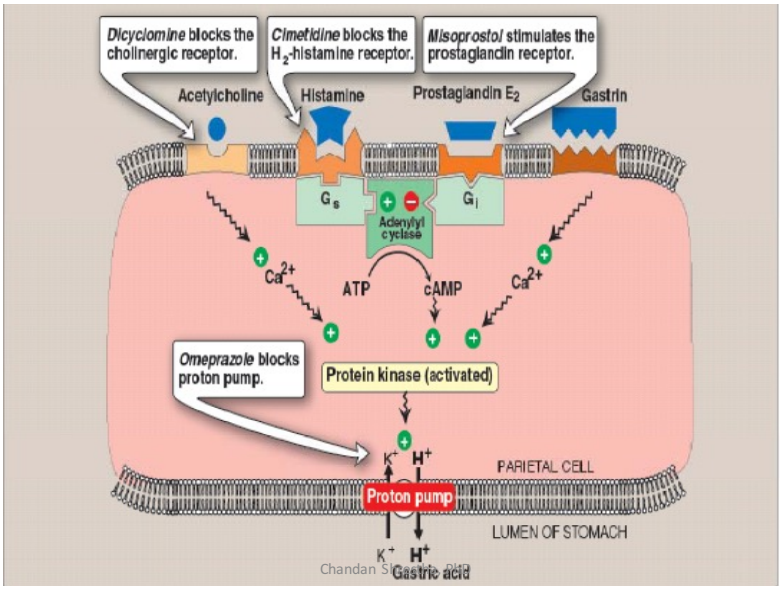
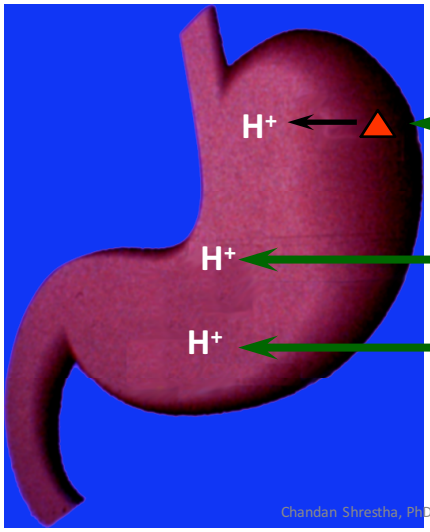
Regulation of HCl secretion



Strategies for Protecting the Gastric Mucosa from Acid Exposure



DRUGS USED IN PEPTIC ULCER

1. Reduction of gastric acid secretion:

a. H_2 anti-histamines: cimetidine, ranitidine, famotidine, roxatidine
b. Proton pump inhibitor: omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole
c. anticholinergics: pirenzepine, propantheline, oxyphenonium
d. Prostaglandin analogues: misoprostol, enprostil, rioprostil

2. Neutralization of gastric acid (antacids)

a. Systemic: sodium bicarbonate, sodium citrate
b. Non systemic: magnesium hydroxide, Magnesium tricilicate, Aluminium hydroxide gel, Magaldrate, Calcium carbonate

3. Ulcer protective: Sucralfate, colloidal bismuth subcitrate (CBS)

4. Anti Helicobacter pylori drugs: amoxicillin, tinidazole, metronidazole, tetracycline, clarithromycin

H_2 Receptor Antagonists

Mechanism of action

- These agents completely inhibit gastric acid secretion induced by histamine.
- They are competitive antagonist of histamine and are fully reversible.
- block the binding of histamine to H2 receptors, reduces the intracellular concentrations of cAMP and, thereby, secretion of gastric acid.

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H_2 Receptor Antagonists

Uses

- Peptic ulcer (Gastric and Duodenal ulcer)
- Zollinger-ellison syndrome
- Stress ulcer
- Gastroesophageal reflux disease

Adverse Effect

- Headache, dizziness, diarrhea, and muscular pain
- Cimetidine inhibits binding of dihydrotestosterone to androgen receptors, inhibits metabolism of estradiol, and increases serum prolactin levels. When used long-term or in high doses, it may cause **gynecomastia or impotence** in men and **galactorrhea** in women.

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Proton Pump Inhibitor

Mechanism of Action

- Irreversibly bind to the H+/K+-ATPase enzyme system (proton pump) of the parietal cell, thereby suppressing secretion of hydrogen ions into the gastric lumen.
- The membrane-bound proton pump is the final step in the secretion of gastric acid.

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Uses:

- Peptic ulcer
- Gastroesophageal reflux disease
- Zollinger-Ellison syndrome
- Acute stress ulcer

Adverse Effect

- nausea, loose stools, headache, dizziness, abdominal pain, muscle and joint pain.

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Anticholinergic Agents (Pirenzepine)

- Blocks the muscarinic receptor in the parietal cells → Decreased intracellular ca^{++} level → Decreased gastric acid secretion.
- Adverse Effect: Dry mouth, blurred vision

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Prostaglandin Analogues (Misoprotol)

- PGE2 and PGI2 are produced in the gastric mucosa and appear to serve a protective role by inhibiting acid secretion and promoting mucus and bicarbonate secretion (cytoprotective effect).
- Indication: Prevention and treatment of NSAIDs induced GI injury.
- Major problems in the use of misoprostol are- diarrhoea, abdominal cramps, uterine bleeding, abortion, and need for multiple daily doses.

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Antacids

- Antacids are basic substances neutralize gastric acid gastric acid and raise the gastric pH
- Antacid also reduce pepsin activity because pepsin is inactive at a pH greater than 4.

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Systemic Antacid

Sodium Bicarbonate

- It is water soluble, acts instantaneously, but the duration of action is short.
- $NaHCO_3 + HCL \longrightarrow NaCL + H_20 + C0_2$

Demerits

- Produces CO_2 in stomach→ distention, discomfort, belching, risk of ulcer perforation.
- Increases Na+ load: may worsen edema and CHF.

Uses

- casual treatment of heartburn: provides quick symptomatic relief.
- Other uses are to alkalinize urine and to treat acidosis.

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Non Systemic Antacid

- **Calcium carbonate** is less soluble and reacts more slowly than sodium bicarbonate with HCl to form carbon dioxide and CaCl2. Like sodium bicarbonate, calcium carbonate may cause belching.
- Formulations containing **magnesium hydroxide or aluminum hydroxide** react slowly with HCl to form magnesium chloride or aluminum chloride and water.
- magnesium salts may cause an osmotic diarrhea and aluminum salts may cause constipation.
- Alum. hydrox. binds phosphate in the intestine and prevents its absorption-**hypophosphatemia** occurs on regular use.

Antacid combinations

- Fast (Mag. hydrox.) and slow (Alum. hydrox.) acting components yield prompt as well as sustained effect.
- Mag. salts are laxative, while alum. salts are constipating: combination may annul each other's action and bowel movement may be least affected.
- Gastric emptying is least affected; while alum. salts tend to delay it, mag. / cal. salts tend to hasten it.

Mucosal Protective Agents

Sucralfate

- It is a basic aluminium salt of sulfated sucrose; binds to positively charged groups in proteins of both normal and necrotic mucosa.
- Sucralfate polymerizes at pH < 4 by cross linking of molecules, assuming a sticky gel-like consistency.
- It preferentially and strongly adheres to ulcer base, especially duodenal ulcer.
- It creates a physical barrier by forming a complex gels with epithelial cells, preventing acid, pepsin from coming in contact with the ulcer base.

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Adverse Effect (few)

- constipation, dry mouth and nausea
- It has potential for inducing hypophosphatemia by binding phosphate ions in the intestine.

Note: Antacids should not be taken with sucralfate because its polymerization is dependent on acid pH.

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Colloidal Bismuth Subcitrate

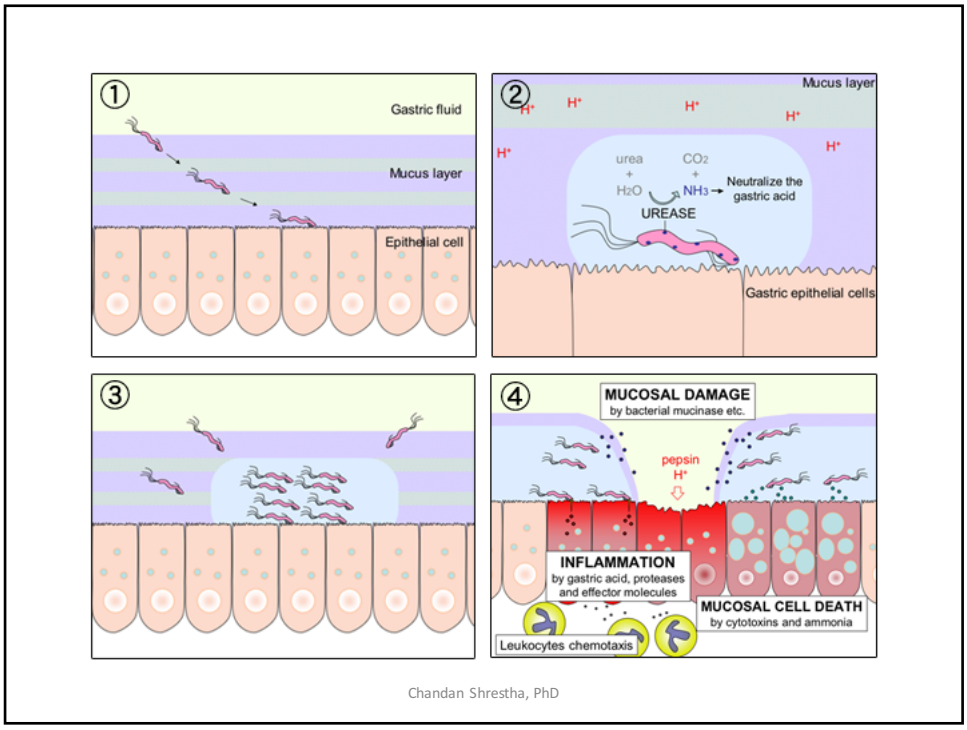
- It is a colloidal bismuth compound; water soluble but precipitates at pH < 5.
- The mechanism of action of CBS is not clear; probabilities are:

1. Increased secretion of mucus and bicarbonate through stimulation of mucosal PGE2 production.
2. CBS and mucus form a glycoprotein-Bi complex which coats the ulcer and acts as a diffusion barrier to HCl.
3. Detaches H. pylori from the surface of mucosa and directly kills this organism involved in causation of ulcers and relapses

- Adverse effect: diarrhea, headache and dizziness.

Anti H. pylori drugs

- H. pylori is a gram negative bacillus uniquely adapted to survival in the hostile environment of stomach.
- It attaches to the surface epithelium beneath the mucus, has high urease activity produces ammonia which maintains a neutral microenvironment around the bacteria, and promotes back diffusion of H+ ions.
- Antimicrobials that have been found clinically effective against H. pylori are: amoxicillin, clarithromycin, tetracycline and metronidazole/ tinidazole.


①
Gastric fluid
Mucus layer
Epithelial cell
②
Mucus layer
H+
urea
CO2
H2O
NH3
Neutralize the gastric acid
UREASE
Gastric epithelial cells
③
④
MUCOSAL DAMAGE
by bacterial mucinase etc.
pepsin
H+
INFLAMMATION
by gastric acid, proteases and effector molecules
MUCOSAL CELL DEATH
by cytotoxins and ammonia
Leukocytes chemotaxis
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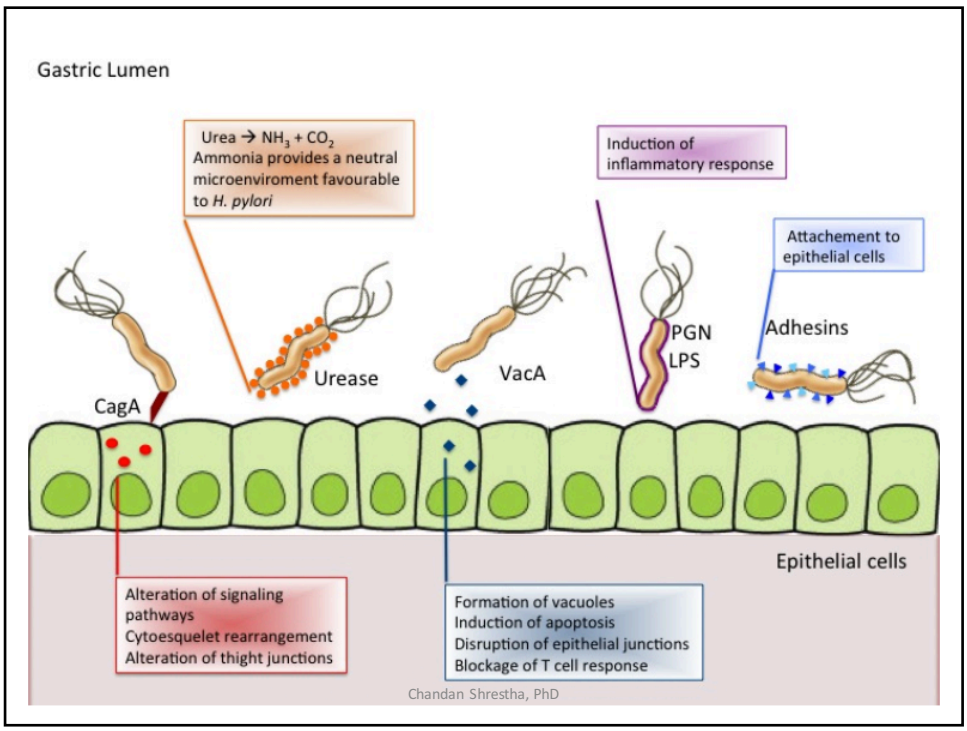
Gastric Lumen
Urea → NH3 + CO2
Ammonia provides a neutral microenviroment favourable to H. pylori
Induction of inflammatory response
Attachement to epithelial cells
CagA
Urease
VacA
PGN
LPS
Adhesins
Epithelial cells
Alteration of signaling pathways
Cytoesquelet rearrangement
Alteration of thight junctions
Formation of vacuoles
Induction of apoptosis
Disruption of epithelial junctions
Blockage of T cell response
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Two week regimens (mg)

1. Amoxicillin 750 + Tinidazole 500 + Omeprazole 20 all BD
2. Amoxicillin 750 + Tinidazole 500 + Lansoprazole 30 all BD
3. Clarithromycin 250 + Tinidazole 500 + Lansoprazole 30 all BD
4. Clarithromycin 500 + Amoxicillin 1000 + Lansoprazole 30 all BD
5. Clarithromycin 500 BD/Amoxicillin 750 BD + Omeprazole 20 BD
6. Amoxicillin 500 TDS/Tetracycline 500 QID + Metronidazole 400 QID/ · Tinidazole 500 BD + Bismuth 120 QID
7. Amoxicillin 750 TDS + Metronidazole 500 TDS + Ranitidine 300 OD
8. Amoxicillin 750 BD + Clarithromycin 250 BD + Lansoprazole 30 BD