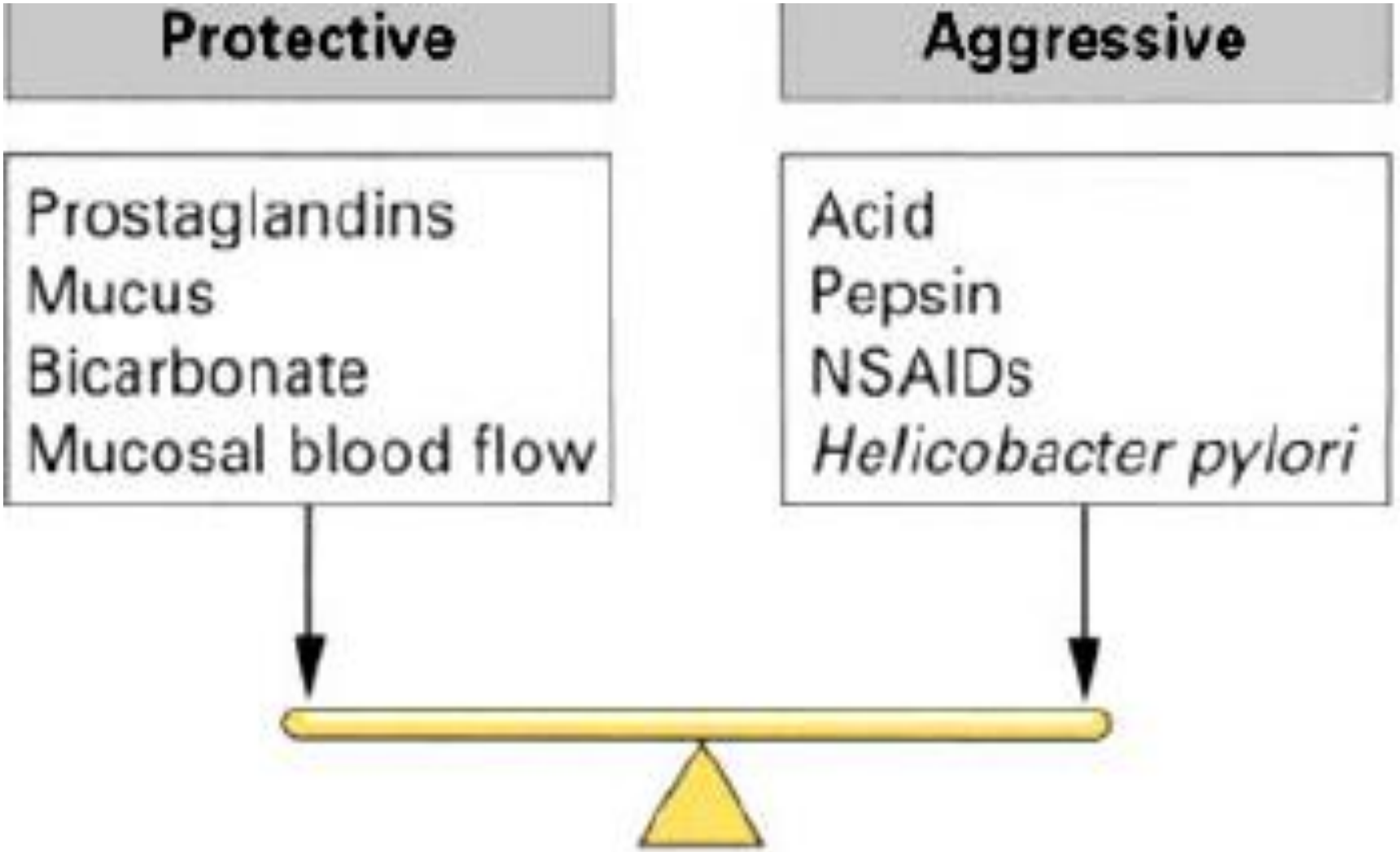
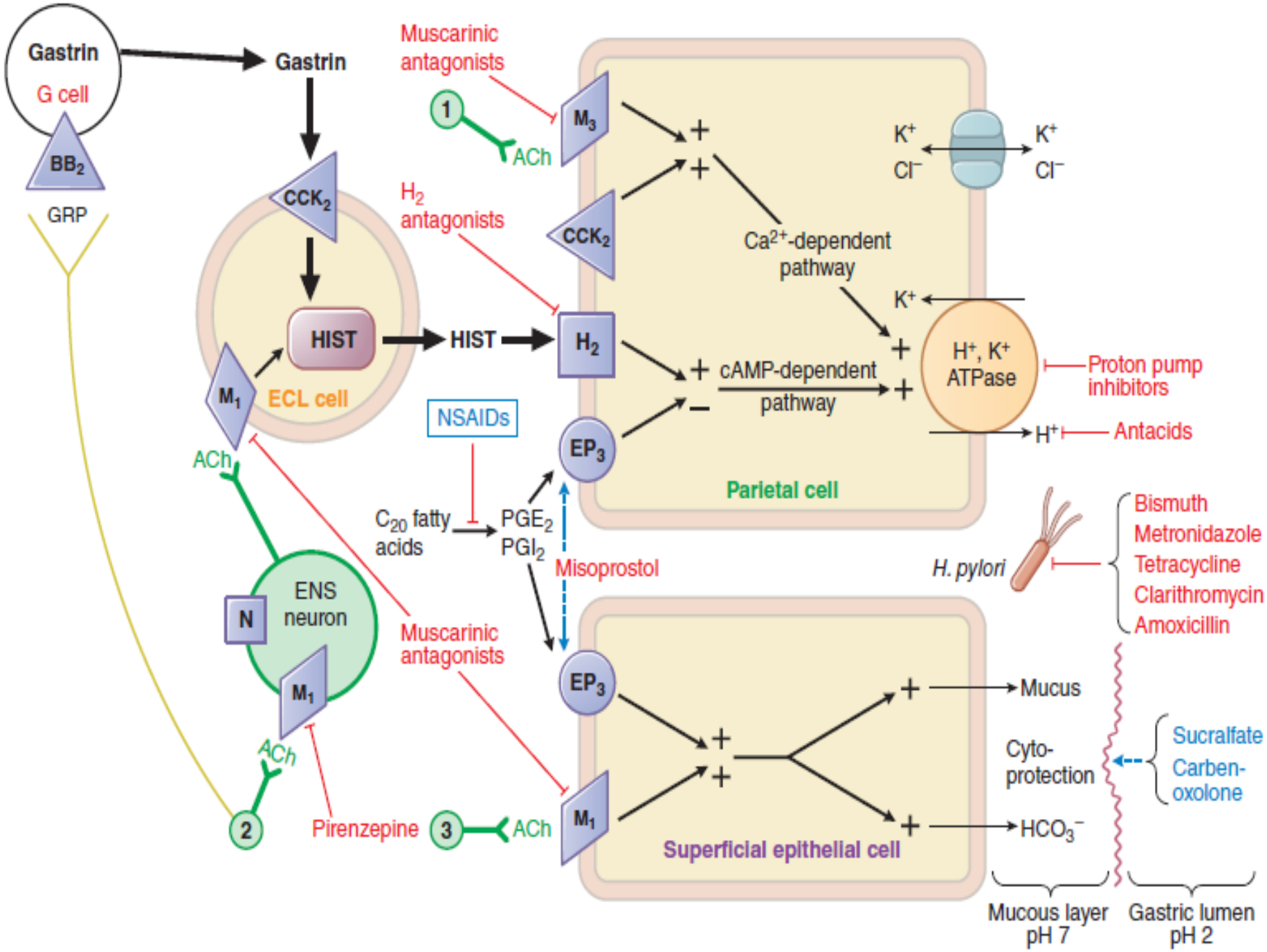
PHARMACOTHERAPY OF PEPTIC ULCER DISEASE




Gastrin
G cell
Gastrin
BB2
GRP
CCK2
HIST
HIST
M1
ECL cell
ACh
Muscarinic antagonists
1
ACh
M3
CCK2
H2 antagonists
H2
EP3
NSAIDs
C20 fatty acids
PGE2
PGI2
Misoprostol
Ca2+-dependent pathway
cAMP-dependent pathway
K+
Cl−
K+
Cl−
K+
H+, K+ ATPase
Proton pump inhibitors
H+
Antacids
Parietal cell
H. pylori
Bismuth
Metronidazole
Tetracycline
Clarithromycin
Amoxicillin
N
ENS neuron
M1
ACh
2
Pirenzepine
Muscarinic antagonists
3
ACh
M1
EP3
Superficial epithelial cell
Mucus
Cyto-protection
HCO3−
Sucralfate
Carben-oxolone
Mucous layer pH 7
Gastric lumen pH 2

REDUCERS OF ACID SECRETION

A. **Proton Pump Inhibitors** : Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole

B. **H2 Receptor Antagonists** : Cimetidine Ranitine, Famotidine, Roxatidine, Lafutidine

C. **Antimuscarinic Drugs** : Pirenzipine, Propantheline, Oxephenonium

NEUTRALIZERS OF SECRETED ACID

Antacids : Hydroxides of Al & Mg, Sodium bicarbonate, Sodium citrate, Simethicone

ENHANCERS OF MUCOSAL RESISTANCE

A. **Prostaglandins** : Misoprostal

B. **Cytoprotective agents** : Sucralfate, Carbenozolone, Bismuth compounds

Rebamipide, Ecabet : Newer agents

ERADICATORS OF H PYLORI INFECTION

Antimicrobial Agents : Tetracycline, Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Colloidal bismuth subcitrate

PROTON PUMP INHIBITORS:

(Irreversible inhibitors of H^+ K^+ ATPase)

Omeprazole
Lansoprazole
Esomeprazole
} enteric coated granules in gelatin capsule

Pantoprazole
Rabeprazole
Omeprazole
} enteric coated tablets

Pantoprazole and Lansoprazole : i.v. injection.

Pharmacokinetics

30 minutes before meals. Food reduces absorption. Hepatic dysfunction reduces clearance of Esomeprazole and Lansoprazole

Adverse Effects

Common: nausea, abdominal pain, diarrhea, constipation, flatulence. Arthralgias, headaches, and skin rashes rare.

Recently a risk of fractures, pneumonia, clostridium difficle diarrhea, hypomagnesemia, vit b12 deficiency, CKD and dementia reported.

Drug interactions

Omeprazole inhibits CYP2C19 (**disulfiram, phenytoin**)

Induces CYP1A2 (**imipramine**, **several antipsychotic drugs**, **tacrine** and **theophylline**).

Chronic treatment (omeprazole) **decreases vitamin B12 absorption**, **reduces bioavailability of ketoconazole**, **ampicillin** esters and **iron salts**

Hypergastrinemia --- frequent and severe --- Rebound hypersecretion of acid upon discontinuation and promotes growth of gastrointestinal tumors.

- Small / inconsistent change in volume of gastric juice, secretion of pepsin and IF.
- No effect on gastric motility.
- Irreversible inhibition --- effects last longer.
- Pretreatment values --- 4-5 days after withdrawal.

Therapeutic Uses

- Gastric and duodenal ulcers , Gastro-esophageal reflux disease (GERD), including erosive esophagitis, heart burn etc.
- Zollinger-Ellison syndrome.
- FDA approved for NSAID associated gastric ulcers in patients who continue NSAID use. Pantoprazole, Lansoprazole, Esomeprazole.
- FDA approved for reducing risk of duodenal ulcer recurrence associated with *H. pylori* infection"

H2 RECEPTOR ANTAGONISTS

Highly selective competitive inhibitors.

Dose dependent inhibition of gastric acid secretion (histamine, caffeine, insulin, protein rich meals and muscarinic drugs)

All phases of gastric secretion are reduced.

Predominantly inhibit basal and nocturnal acid secretion.

Do not affect gastric emptying, lower esophageal tone and pancreatic secretions.

Adverse Reactions

Minor

Diarrhea, headache, drowsiness, fatigue, muscular pain and constipation.

Rarely : CNS (confusion, delirium, hallucinations, slurred speech and headaches)

Cimetidine --- (high doses) decreases testosterone binding to androgen receptor

Inhibits hydroxylation of estradiol; Galactorrhea in women ; gynecomastia, reduced sperm count and impotence in men.

Blood dyscrasias

Thrombocytopenia.
No major teratogenic risk.

Drug interactions

Cimetidine inhibits CYPs (*e.g.*, CYP1A2, CYP2C9, and CYP2D6)
Slight increases in blood alcohol concentration from concomitant use

Therapeutic Uses

Gastric and duodenal ulcers, uncomplicated GERD, prevention of stress ulcers.

Tolerance and Rebound With Acid-Suppressing Medications

Within 3 days of starting treatment --- secondary hypergastrinemia --- stimulate histamine release from ECL cells.

Tolerance generally observed with H2 receptor blockers.

Rebound increases in gastric acidity when discontinued --- gradual drug taper required.

PROSTAGLANDIN ANALOGS

Prostaglandin E2 (PGE2) and prostacyclin (PGI2) : decrease gastric acid secretion.

PGE2 : cytoprotective effects --- stimulation of mucin and HCO_3 secretion and increased mucosal blood flow

MISOPROSTAL

Synthetic analog of PGE1 --- reduces NSAID induced mucosal damage --- increased potency, duration of antisecretory effect, oral bioavailability and safety.

The degree of inhibition dose related ; for prophylaxis 200 µg four times a day.

Misoprostol acid : **active metabolite**.

Food and antacids decrease misoprostol absorption

Adverse Effects

Diarrhea, abdominal pain and cramps (dose-related).

Avoid in inflammatory bowel disease.
Contraindicated in pregnancy.

SUCRALFATE : (octasulfate of sucrose + $Al(OH)_3$)

At pH < 4 undergoes cross-linking --- viscous, sticky polymer --- **adheres to epithelial cells / ulcer craters**.

Inhibits hydrolysis of mucosal proteins by pepsin.

- **Stimulation of local production of prostaglandins** and epidermal growth factor
- **Binds bile salts** ; treats syndromes of bilary esophagitis or gastritis.

Therapeutic Uses

- Prophylaxis of **stress ulcers**
- Mucosal inflammation / ulceration not responding to acid suppression --- **oral mucositis** (**radiation** and **aphthous ulcers**)
- Bile reflux gastropathy
- **Radiation proctitis** and **solitary rectal ulcers**

Take on empty stomach 1 hour before meals. Avoid antacids within 30 minutes of dose.

Dose : 1 g four times daily (for active ulcer) or 1 g twice daily (for maintenance therapy).

Adverse Effects

- Constipation (about 2%)

- Avoid in renal failure (aluminum overload)
  Not combined with Aluminum antacids.

- Inhibits absorption : phenytoin, digoxin, cimetidine, ketoconazole and fluoroquinolone antibiotics

- Bezoars Develop : in patients with gastroparesis.

ANTACIDS

$NaHCO_3$: water-soluble, rapidly absorbed from stomach, sodium overload --- risk in cardiac / renal failure.

$CaCO_3$: CO2 released from bicarbonate / carbonate antacids --- belching, nausea, abdominal distension and flatulence.

Combination of **Mg2+** (rapidly reacting) and **Al3+** (slowly reacting) **hydroxides** : balanced and sustained neutralizing capacity.

Uncomplicated ulcers --- orally 1 and 3 hours after meals and at bedtime.
Severe symptoms /uncontrolled reflux: every 30 to 60 minutes. Suspension form prefered.

Adverse effects
Elevate urinary pH by one pH unit.
Absorbed Al3+ --- problem in renal dysfunction

Absorbed Ca --- transient hypercalcemia.

Milk-alkali syndrome
Altered gastric and urinary pH
Insoluble complexes

OTHERS

M1 receptor antagonists

Suppress neural stimulation of M_1 receptors. Relatively poor efficacy, significant and undesirable anticholinergic side effects ; risk of blood disorders (pirenzepine)

Rebamipide: increase prostaglandin generation, scavenges reactive oxygen species.

Ecabet : increases PGE2 and PGI2

Carbenoxolone : alters composition and quantity of mucin. ADR: Hypokalemia and hypertension.

Bismuth compounds :

Help eradicate H. Pylori, prevent ulcer recurrence ; Bind to base of ulcers, promote mucin and bicarbonate production.

Treatment of Helicobacter pylori Infection.

Single-antibiotic regimens are ineffective.

Proton pump inhibitors, H_2 receptor blockers enhance effectiveness of antibiotics

10 to 14 days regimen appears better than shorter treatment regimens

Drawbacks

(i) Poor patient compliance

(ii) Medication-related side effects

(iii) Inconvenience of 3 or 4 drug regimens administered several times a day.

Package that combines daily doses into one unit --- improve patient compliance

Emergence of resistance to clarithromycin and *metronidazole* ; failure to eradicate.

TripleTherapy for Helicobacter pylori

For 14 days*:* **[**Proton pump inhibitor + clarithromycin 500 mg + (metronidazole 500 mg or amoxicillin 1 g)**]** twice a day. (Tetracycline 500 mg can be substituted for Amoxicillin or Metronidazole.)

Quadruple-drug regimen for H pylori

For 14 days : Proton pump inhibitor twice a day + Metronidazole 500 mg three times daily + (Bismuth subsalicylate 525 mg + Tetracycline 500 mg four times daily)

The US-FDA approved regimen is:
Lansoprazole 30 mg + Amoxicillin 1000 mg + clarithromycin 500 mg, all given twice daily for 2 weeks.

National Formulary of India (NFI, 2010) suggests a model H. pylori eradication regimen of 1 week consisting of:

- Omeprazole 40 mg OD + Metronidazole 400 mg TDS + Amoxicillin 500 mg TDS.

Quadruple therapy × 14 days:
H2-receptor antagonist twice a day + (bismuth subsalicylate 525 mg + metronidazole 250 mg + tetracycline 500 mg) four times day

Gastroesophageal Reflux Disease (GERD):

- Approach depends upon severity.
- Dose individualised for symptom control.
- Strictures respond better to proton pump inhibitors than to H2-receptor antagonists

Mild GERD symptoms : Antacids and / or nocturnal doses of H2-receptor antagonists, twice-daily dosing in moderate cases.

Prokinetic agents: not useful either alone or in combination with acid-suppressant agents.

Chronic disorder ; long-term therapy

1. **"step-down" approach** --- maintains symptomatic remission --- decrease dose of the proton pump inhibitor or switch to an H2-receptor antagonist.

2. **Intermittent "on-demand" therapy** with proton pump inhibitors (symptomatic relief in those who responded initially but continue to have symptoms)

GERD and Pregnancy: Heartburn (30% to 50% of pregnancies)

Mild cases of GERD --- Conservative treatment Antacids or sucralfate, if symptoms persist, H2-receptor blocker.

Proton pump inhibitors for severe symptoms.

Peptic Ulcer Disease

Duodenal ulcer --- more acid at night (basal secretion)

Gastric ulcer --- normal or even diminished acid production

60% of peptic ulcers --- *H. Pylori* infection.

NSAIDs --- bleeding peptic ulcers.

Topical injury --- minor role in pathogenesis --- effects mediated systemically.

DRUG : ACTIVE ULCER / MAINTENANCE THERAPY
H 2 -Receptor Antagonists

Cimetidine 800 mg at bedtime/400 mg twice daily (400 mg at bedtime)

Famotidine 40 mg at bedtime (20 mg at bedtime)

Nizatidine/ranitidine 300 mg after evening meal or at bedtime/150 mg twice daily (150 mg at bedtime)

Proton Pump Inhibitors

Lansoprazole

15 mg daily(DU; NSAID risk reduction)

30 mg daily (GU; NSAID-associated)

Omeprazole 20 mg daily

Rabeprazole 20 mg daily

Prostaglandin Analogs

Misoprostol 200 ug four times daily (NSAID-associated ulcer prevention)*

*Only misoprostol 800 ug/day reduces risk of ulcer complications such as perforation, hemorrhage, or obstruction

NSAID-Related Ulcers

Chronic users --- 2 - 4% risk of ulcer, GI bleeding or perforation.

Healing despite continuous use with acid suppressant agents --- higher doses and longer duration than standard regimens (e.g. 8 weeks).

Proton pump inhibitors superior to H_2 receptor antagonists and misoprostol in promoting healing of active ulcers and preventing recurrence.

Stress-Related Ulcers.

Intravenous H2-receptor antagonists / **Intravenous proton pump inhibitors** reduce incidence of GI hemorrhage.

Risk of pneumonia secondary to gastric colonization by bacteria in an alkaline environment.

Sucralfate --- prophylaxis against bleeding without increasing the risk of aspiration pneumonia.

Zollinger-Ellison Syndrome

Proton pump inhibitors; at twice routine dosage.

Nonulcer Dyspepsia

Associated with gastritis (with or without *H.* pylori) or with NSAID use ; pathogenesis controversial.

Empirical treatment with acid-suppressive agents is used.