Drugs used to treat asthma

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ASTHMA

Asthma - a chronic lung-disease that inflames and narrows the airways in response to stimuli.

The patient has intermittent attacks of :
dyspnoe, wheezing, and cough and disorder of breathing
Its pathologic features are:
. contraction of airway smooth muscle,
. mucosal thickening from edema and
. cellular infiltration, viscid plugs of mucus

Epidemiology

- according to epidemiological studies asthma affects 1-18% of population of different countries
- in 2006 more than 300 million patients with asthma all over the world
- 250 thousands of patients die of asthma
- Asthma is the most common chronic disease among children.

Asthma severity classification

Clinical course, severity	Daytime asthma symptoms	Nighttime awakenings	FEV1, PEF
Intermittent	< 1 /week	2 and < /month	>80% predicted. Daily variability < 20%
Mild persistent	≥ 1 /week but not daily	> 2 /month	>80% predicted. Daily variability – 20-30%
Moderate persistent	Daily	> 1 /week	> 60 but < 80% predicted. Variability>30%.
Severe persistent	Persistent, which limit normal activity	Daily	<60% predicted. Variability > 30%.

Causes of asthma

While the exact cause of asthma is not known, it is thought that a variety of factors interacting with one another, early in life, result in the development of asthma.

Causes – cont.

- parents with asthma
- atopy
- childhood respiratory infections
- exposure to allergens or infections while the immune system is developing

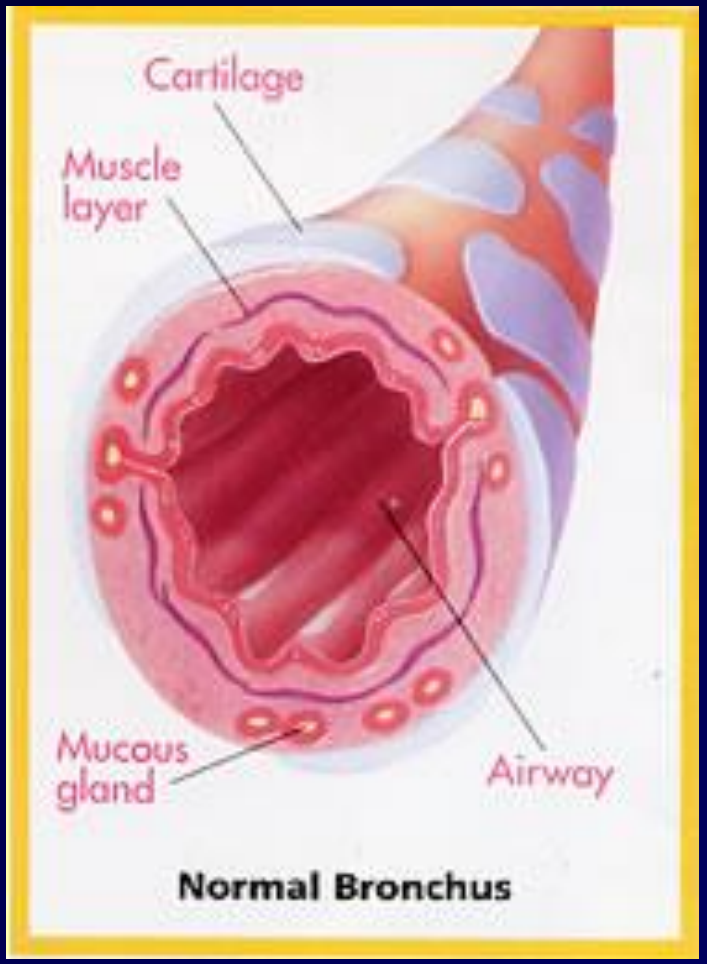
Asthma trigers

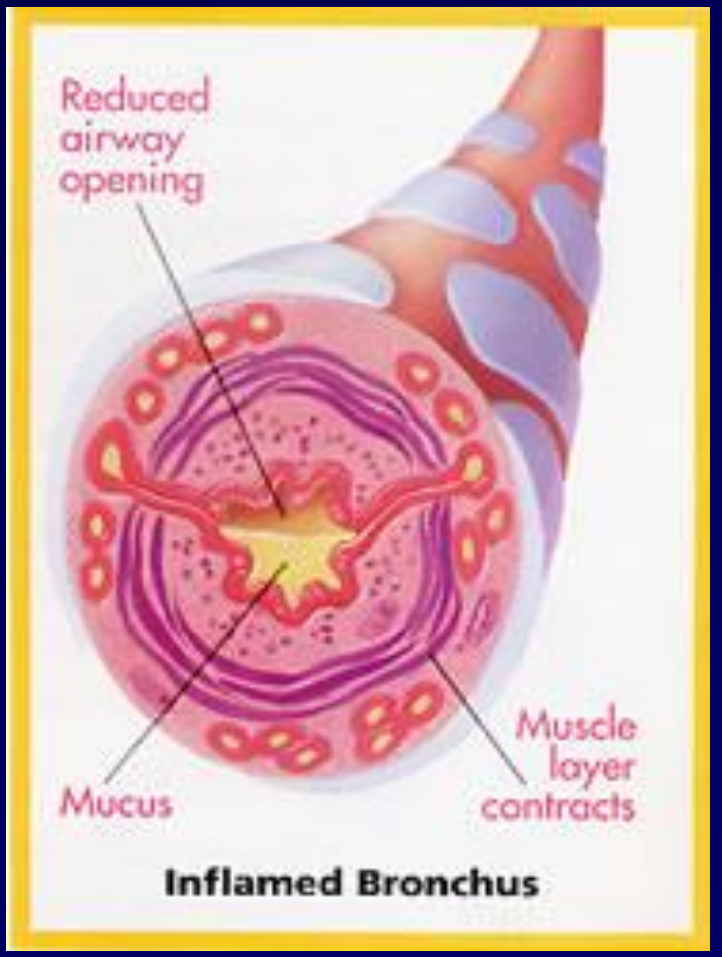
- allergens – pollen and household dust
- air pollutants – solvents
- respiratory infection
- stress – exercise in dry & cold climates
- chemicals – drugs (aspirin)
- food – shellfish & nuts

Asthma Symptoms

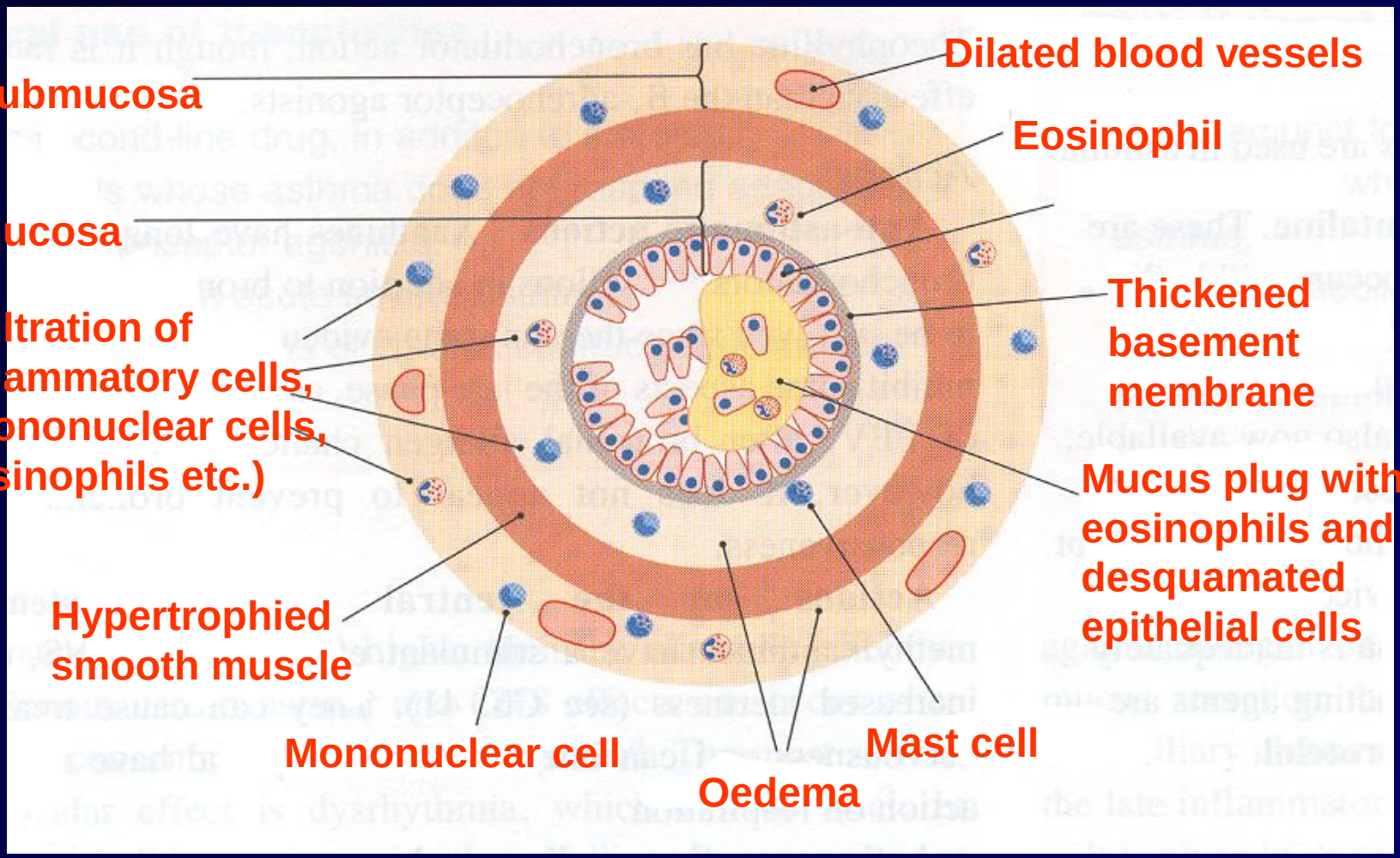
- coughing
- shortness of breath
- tightness in your chest
- wheezing
- breathing faster
- itchy or sore throat

Pathology


Cartilage
Muscle layer
Mucous gland
Airway
Normal Bronchus


Reduced airway opening
Mucus
Muscle layer contracts
Inflamed Bronchus

Schematic diagram of a cross-section of a bronchiole showing the changes that can occur with severe chronic asthma.



- **airway obstruction, contraction of smooth muscle is most easily reversed by BRONCHODILATORS**

- **edema and cellular infiltration requires sustained treatment with ANTI-INFLAMMATORY AGENTS.**

Antiasthmatic drugs

Bronchodilators

(Quick relief medications)

treat acute episodic attack of asthma

- **SABA**
- **Antimuscarinics**
- **Xanthine preparations**

Anti-inflammatory drugs

(control medications or prophylactic therapy)

reduce the frequency of attacks

- **Corticosteroids**
- **Mast cell stabilizers**
- **Leukotrienes antagonists**
- **Anti-IgE mab**
- **LABA**

Drugs for asthma treatment

Antiinflammatory drugs

Bronchodilators

Antiasthmatic agents are often used by :

inhalation

- aerosol
- dry powder

orally

i.v.

Medications to Treat Asthma: How to Use a Spray Inhaler

Remember to breathe in slowly.

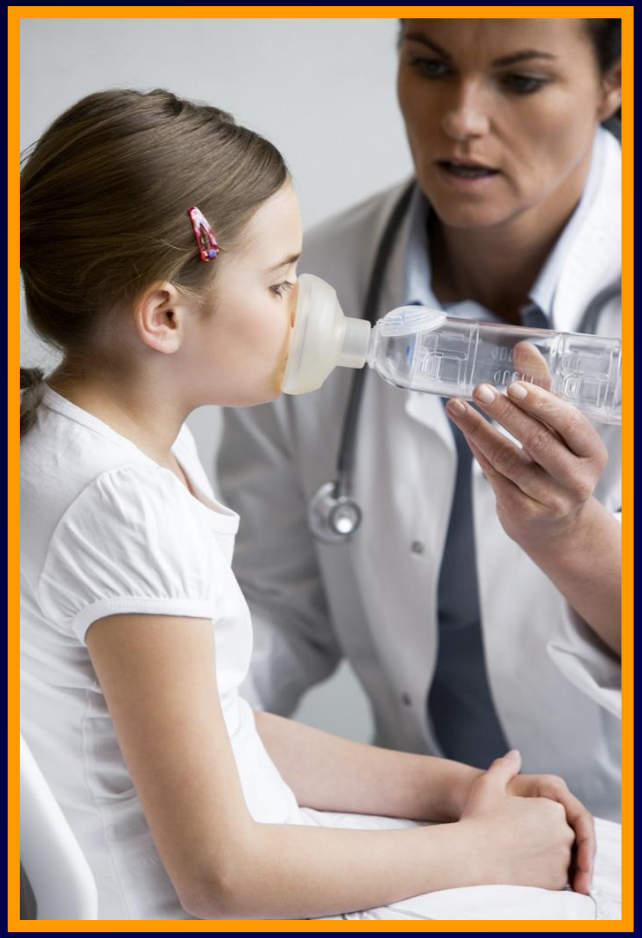
1. Take off the cap.
   Shake the inhaler.

2. Stand up.
   Breathe out.

3. Put the inhaler in your mouth or put it just in front of your mouth. As you start to breathe in, push down on the top of the inhaler and keep breathing in slowly.

4. Hold your breath for 10 seconds.
   Breathe out.

Medications to Treat Asthma: Inhalers and Spacers



Spacers can help patients who have difficulty with inhaler use and can reduce potential for adverse effects from medication.

Nebulizer

Inhaler

ANTIINFLAMMATORY DRUGS

Corticosteroids

Antileukotriens

Inhibitors of mast cell degranulation

Corticosteroids

Corticosteroids

- The role of corticosteroids in asthma, and respiratory care in general, is to combat inflammation of the airways associated with certain respiratory conditions.

- Corticosteroids indirectly prevent inflammation-mediated bronchoconstriction through the inhibition of prostaglandins and leukotrienes synthesis.

- In addition, corticosteroids reverse vascular permeability associated with the inflammation process.

Corticosteroids administered p.o. or i.v.

Because of *severe adverse effects* (p.o. or i.v.) are generally reserved for patients:

who do *not improve adequately with* inhalatory corticosteroids

Treatment: *oral dose of 30-60 mg of* prednisone *per day.*

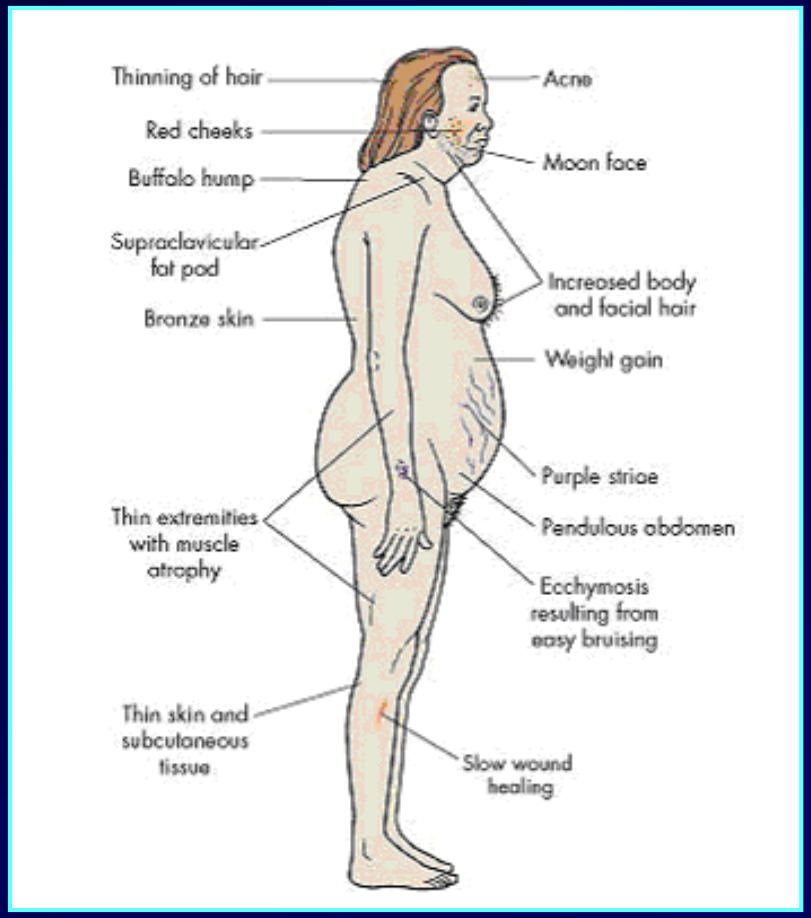
In most patients, systemic corticosteroids can be discontinued in a week or 10 days

Systemic adverse effects of glucocorticoids administered p.o. or i.v.

- hyperglycemia
- hypertension
- immunosuppresion
- adrenal suppresion
- osteoporosis
- growth retardationin children
- cataract
- glaucoma

CUSHING SYNDROM

CUSHING SYNDROME



Corticosteroids administered by inhalation

The most effective method of decreasing systemic adverse effects due to corticosteroid therapy is to administer the drug as an aerosol or powder by inhalation.

Inhaled corticosteroids (ICS)

- are currently the most effective long-term preventive medications

- early diagnosis and treatment are important prevention of airway remodelling

- long-term treatment with minimal daily doses of ICS

corticosteroids for inhalations are: beclomethasone, budesonide, and fluticasone with minimal systemic absorption and reduced adverse effects.

An average daily dose - from 100-2000 μg/day inhalation according to asthma severity.

<u>Systemic steroid effects</u> are minimal if compared with those of the oral prednisone: oropharyngeal candidiasis - mouthwashes can alleviate this problem

ICS and the growth in children

Long-term and retrospective studies proved that treatment with ICS (BUD 200-800 μg/day) does not significantly influenced the growth.

Chronic use of inhaled corticosteroids:

- effectively reduces symptoms and improves pulmonary function in patients
- reduces bronchial hyperreactivity
- the maximal reduction may not be achieved until 9-12 months of therapy

Inhalation has very less side effects:

- Oropharyngeal candidiasis
- Dysphonia (voice hoarseness)

Withdrawal

- Abrupt stop of corticosteroids should be avoided and dose should be tapered (*adrenal insufficiency syndrome*).

Antileukotriens

- leukotrienes are strong chemical mediators of bronchoconstriction and inflammation
- increase mucous secretion and mucosal edema
- formed by the 5-lipoxygenase pathway of arachidonic acid metabolism in response to cellular injury
- are release more slowly than histamine

Cysteinyl leukotriene-receptor antagonists

Montelukast, pranlukast

- **prevent antigen-induced and exercise- induced asthma**
- **relax the airways in mild asthma, they effect is additive to β_2 adrenoceptors agonists**

5-lipoxygenase inhibitors

Zileuton prevent the production not only LTC_4 and LTD_4 but also LTB_4 a chemotaxin that recruits leukocytes into the bronchial mucosa and then activates them

Inhibitors of mast cell degranulation

Sodium cromoglycate

- inhibition of mast cell degranulation
- inhibition of inflammatory cells
- very good effectivity in children
- 4-6 week of therapy
- in prevention

Clinical use:

- reversible bronchospasm
- asthma bronchiale (alergic)
- allergic rhinitis, conjuctivitis

Unwanted effects:

Rare: cought, bad taste, headache

Sodium nedocromil

- inhibition of mast cell degranulation
- inhibition of inflammatory cells (IC)
- inhibition of IC cummulation in bronchial mucosa
- prevention of immediate an late bronchoconstr.
- decrease of bronchial hyperreactivity

Clinical use:

- prevention of astma (allergic, non-aller.)
- excersise induced asthma

Unwanted effects:

- bad taste, headache

New Treatments

Monoclonal Anti-IgE Antibody

Omalizumab

- it inhibits the binding of IgE to mast cells and basophils

- it inhibits the activation of IgE already bound to mast cells and prevents their degranulation

- it is indicated for asthmatic patients who are not adequately controlled by inhaled GCS and who demonstrate sensitivity to aero-allergens

ADRs: anaphylaxis, fever, arthralgia, and rash, malignancy

Monoclonal anti-IL-5 antibody

Reslizumab

- it binds to IL-5 with and inhibits IL-5 signaling

- IL-5 - cytokine responsible for the differentiation, maturation, recruitment and activation of human eosinophils

- treatment of severe asthma in patients aged 18 years and older, with an eosinophilic phenotype

- ADRs: mouth and throat pain, muscle pain and fatigue, anaphylaxis

Monoclonal anti-IL-5 antibody

Mepolizumab

- it binds to IL-5 and prevents it from binding to its receptor (specifically to α-subunit) on the surface of eosinophils

- treatment of severe asthma in patients aged 12 years or older and with an eosinophilic phenotype in combination with other antiasthmatics

- ADRs: headache, reactions at the site of injection, infections of the urinary and lower respiratory tract eczema and muscle spasms

BRONCHODILATORS

1. Sympathomimetic agents

2. Muscarinic antagonists

3. Methylxanthines

4. Magnesium

Sympathomimetic drugs

Mechanism of Action

- direct β_2 stimulation ⇨ stimulate AC ⇨ ⇧ cAMP ⇨ bronchodilation

- inhibit mediators release from mast cells

- increase mucus clearance by ⇧ ciliary activity

Sympathomimetic agents

Nonselective

Adrenaline is an effective, rapidly acting bronchodilator when injected *subcutaneously* (1:1000 solution) *or inhaled* as a microaerosol. Maximal bronchodilation is achieved 15 minutes after inhalation and lasts for 60-90 minutes.

Adverse effects: *tachycardia, arrhythmias, and worsening of angina pectoris*

β_2-selective agonist

the most widely used drugs for the treatment of asthma

salbutamol, terbutaline, fenoterol

Bronchodilation begins in 5 minutes, is maximal by *30-60 minutes and persists for 2 hours.*

Bronchial deposition *depends on the particle size*. *Even with particles in the optimal size range of* 2-5 μm, 70-50% of the total dose is deposited in the mouth or pharynx.

β_2-selective agonist - cont.

Terbutaline is also prepared in *tablet form*.
One tablet 3 times daily is the usual regimen.

Newer β_2-selective agonists

developed for *an increased duration of action* (12 hours or more) vs. older β_2 agonists (4-6 hours) include:

formoterol, salmeterol (for inhalation)
clenbuterol, procaterol (per os)

Their high lipid solubility permits them to dissolve in the smooth muscle cell membrane and reach high concentration "slow release depot" that provides the drug available to beta receptors over a long period.

Adverse effects of β agonists

- cardiac arrhythmias from β_1-receptor stimulation
- muscle tremor
- headache and insomnia
- flushing

Muscarinic antagonists

- muscarinic antagonists competitively inhibit the effect of ACh at M-*receptors*
- ipratropium, tiotropium
- used for patients with heart disease or thyreotoxicosis in whom β agonists are unsuitable

Methylxanthines

Theophylline, theobromine, and caffeine (alkaloids from tea, cocoa, and coffee)

Central nervous system effects

increased alertness, tremor and nervousness, stimulant effects on respiration

Cardiovascular effects

stimulation of the heart (possitive chronotropic and inotropic actions)

Effects on the GIT

spasmolytic action, increase in HCl secretion

Effects on kidney

weak diuretic effect, involving both increased GF and reduced reabsorption in the tubules

Effects on smooth muscle

vasodilation, bronchodilation

Clinical use of methylxanthines

Theophylline is used as a theophylline salt - **aminophylline**, which contains 86% of theophylline

Improvements in theophylline preparations: anhydrous theophylline in a microcrystalline form in which the increased surface area facilitates solubilization for complete and rapid absorption after oral administration.

Theophylline blood level should be m o n i t o r e d.
Therapeutic and toxic effect of theophylline are related to the plasma concentrations of the drug.
Improvement in pulmonary function is well correlated with plasma concentration in the range o
5-20 mg/L.
Anorexia, nausea, vomiting, abdominal discomfort, headache, and anxiety become common at concentrations greated than 20 mg/L.
Higher* levels (> 40 mg/L) may cause *seizures* or *arrhythmias,
these may not be preceded by gastrointestinal or neurologic warning symptoms.

Drug-drug interaction

the half-life of theophylline

- is increased by *erythromycin, cimetidine ciprofloxacin, oral contraceptives*

- is decreased by concurrent use of *phenytoin, carbamazepine, rifampicin and phenobarbital*

several sustained-release preparations with

aminophylline and theophylline

are available and can produce therapeutic blood levels of theophylline for up to 12 or 24 hours.

These preparations offer the advantages of

- **less frequent drug administration,**
- **less fluctuation of theophylline blood levels,**
- **more effective treatment of nocturnal bronchospasm.**

Use of Magnesium for Acute Asthma

- Acts as smooth muscle relaxer & suppresses neutrophil burst response
- Clearly safe & few side effects
- 2.0 to 5.0 gm IV dose reasonable to try for :
  - Severe symptoms
  - Respiratory failure
  - Non-response to standard Rx

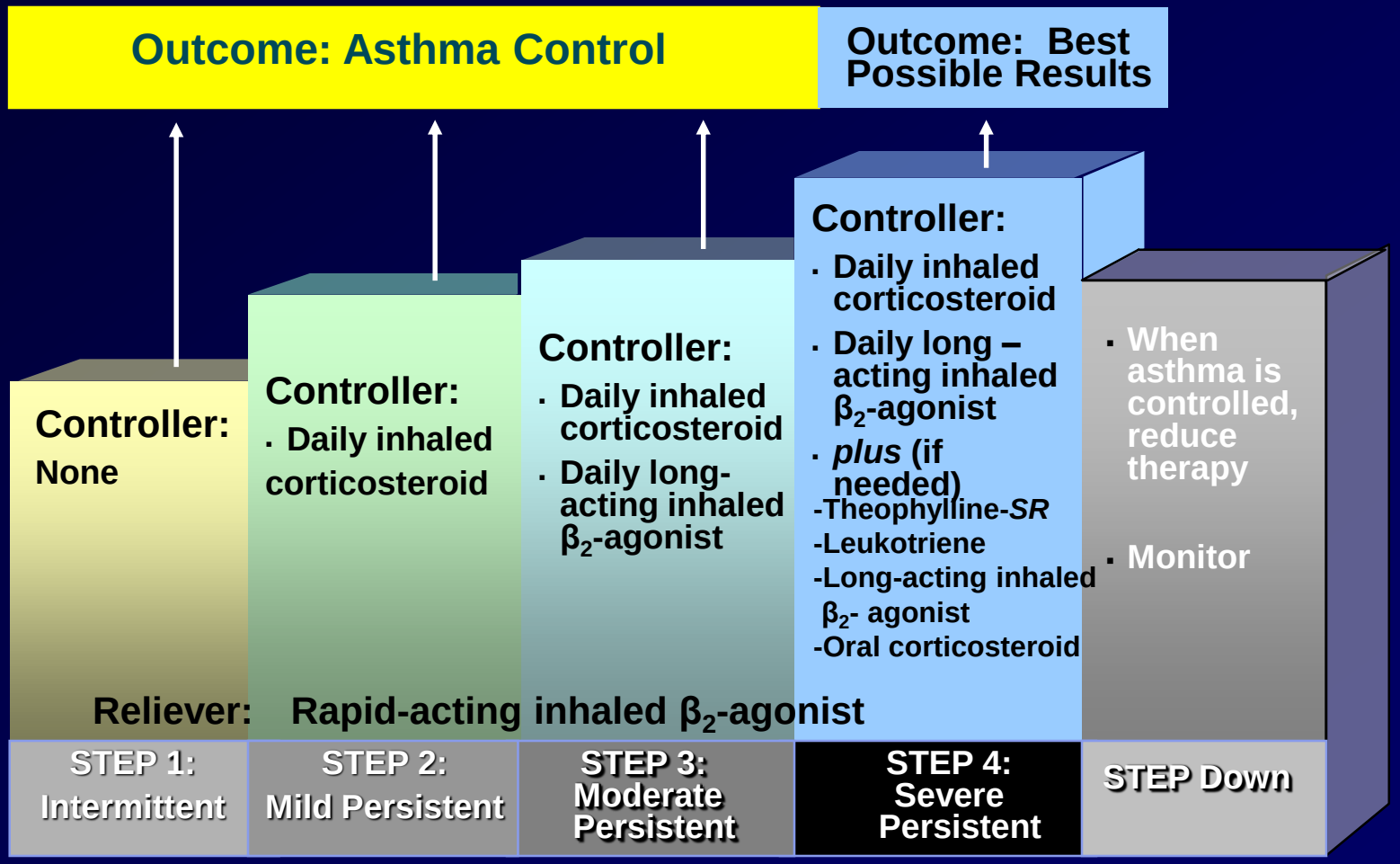
Medications to Treat Asthma: Long-Term Control

- Taken daily over a long period of time
- Used to reduce inflammation, relax airway muscles, and improve symptoms and lung function
  - Inhaled corticosteroids
  - LABA
  - Leukotriene modifiers

Medications to Treat Asthma: Quick-Relief

- Used in acute episodes
- Generally SABA
- Ipratropium, tiotropium
- Oral and i.v. GC

Stepwise Approach to Asthma Therapy - Adults



Chronic Obstructive Pulmonary Disease (COPD)

- Refers to triad of disease processes :
  - Asthma (airway reactivity)
  - Bronchitis (airway inflammation)
  - Emphysema (airway collapse)
  - All 3 coexist to some degree in same pt.

Chronic bronchitis

- chronic cough with sputum production for at least 3 months / yr. for at least 2 yrs.

Emphysema

- enlargement of distal air passages due to alveolar septal destruction (& obliteration of pulm. capillary bed)

Signs Associated with COPD Exacerbations

- Dyspnea
- Tachypnea
- Tachycardia
- Cyanosis
- Diaphoresis

Management of COPD Exacerbations

- For ALL Pts.:
  - Oxygen
  - Beta agonist
  - Anticholinergic
- For some pts.:
  - Corticosteroids
  - Antibiotics
  - Diuretics

New Treatments

Roflumilast - selective, long-acting inhibitor of the phosphodiesterase-4 (PDE-4)

- it has anti-inflammatory effects

- primary clinical use is in the prevention of exacerbations in severe COPD

- ADRs: diarrhea, weight loss, nausea, headache, insomnia

Antitussives

Cough physiology

Cough reflex

- induces coughing and expectoration
- initiated by irritation of sensory receptors in the respiratory tract

To remove secretions or foreign objects

Two basic types of cough

- productive cough

  removes excessive secretions

- nonproductive cough

  dry cough

Coughing

- most of the time, coughing is beneficial

  removes excessive secretions

  removes potentially harmful foreign substances

In some situations, coughing can be harmful, such as after hernia repair surgery

Definition

- drugs used to stop or reduce coughing

- opioid and nonopioid

Used only for *nonproductive* coughs!

Mechanism of Action

Opioids

- suppress the cough reflex by acting on the cough center in the medulla

- examples:

- **codeine**
- **hydrocodone**
- **pholcodine**

Codeine

An opium alkaloid similar to morphine

- less potent than morphine as analgesic and respiratory depressant.
- 60% effective orally.
- A standard antitussive
- A small fraction of administered codeine is metabolized to morphine which is responsible for analgesic effects of codeine.

MOA of Codeine:

- Directly suppresses cough centre in Medulla.
- Suppresses cough for about 6 hrs.

Adverse effects of Codeine:

- In therapeutic doses minimum side effects
  - Sedations, nausea, constipation
- At higher doses respiratory depression and drowsiness can occur.
- Contraindicated in asthmatic patients.
- Can cause tolerance and dependance.

Pholcodine

- Pholcodeine has similar efficacy as codeine with longer duration of action of 12hrs

- It has no analgesic or addiction property
- No euphoria

Mechanism of action (cont'd)

Nonopioids

- suppress the cough reflex by preventing the cough reflex from being stimulated

examples:

- **benzonatate**
- **dextromethorphan**
- **butamirate**

Indications

Used to stop the cough reflex when the cough is nonproductive and/or harmful

Side effects

benzonatate

- dizziness, headache, sedation, nausea,

dextromethorphan

- dizziness, drowsiness, nausea

opioids

- sedation, nausea, vomiting, constipation, urinary retention

Expectorants

Definition

by increasing the production of respiratory tract fluids, expectorants reduce the thickness, adhesiveness, and surface tension of mucous, making it easier to clear from the airways

Mechanisms of action

- direct stimulation
- reflex stimulation

Final result: thinner mucus
that is easier to remove

Mechanism of action (cont'd)

Reflex stimulation

- agent causes irritation of the GI tract

- secretions occur in response to this irritation

Example: guaifenesin

Mechanism of action (cont'd)

Direct stimulation

- the secretory glands are stimulated directly to increase their production of respiratory tract fluids

Examples: iodine-containing products such as iodinated glycerol and potassium iodide

Indications

- used for the relief of coughs from: colds, minor bronchial irritation, bronchitis, influenza, sinusitis, bronchial asthma, emphysema, and other respiratory disorders

Common side effects

guaifenesin

- nausea, vomiting, gastric irritation

iodinated glycerol

- GI irritation, rash, enlarged thyroid gland

potassium iodide

- nausea, vomiting, bad taste

MUCOLYTICS

MUCOLYTICS

- act directly on mucous, breaking down sticky, thick secretions so they're more easily eliminated

MUCOLYTICS

Bromhexine

- potent mucolytic and mucokinetic agent

- depolymerises mucopolysaccharides directly or by liberating of lysosomal enzymes – network of fibres in tenacious sputum is broken

- side effects: lacrimation, rhinorrhea, gastric irritation, hypersensitivity

MUCOLYTICS

Ambroxol

– metabolite of bromhexine

- simmilar effects and side effects

Acetylcysteine

- it opens disulfide bonds in mucoproteins present in sputum

- it has to be administered directly into respiratory tract

- antidotum in paracetamol overdose

Gastrointestinal drugs

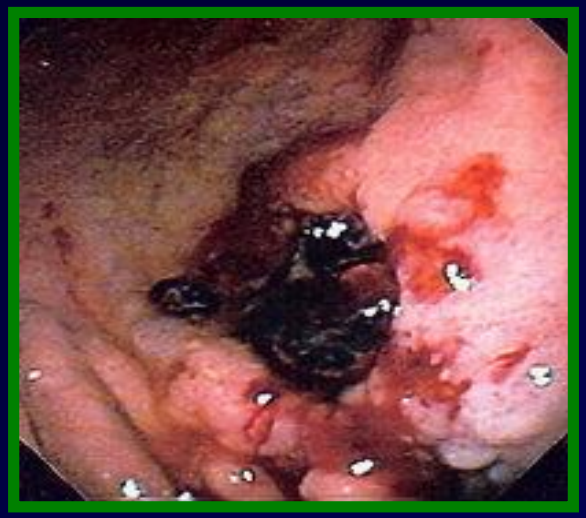
Peptic ulcer

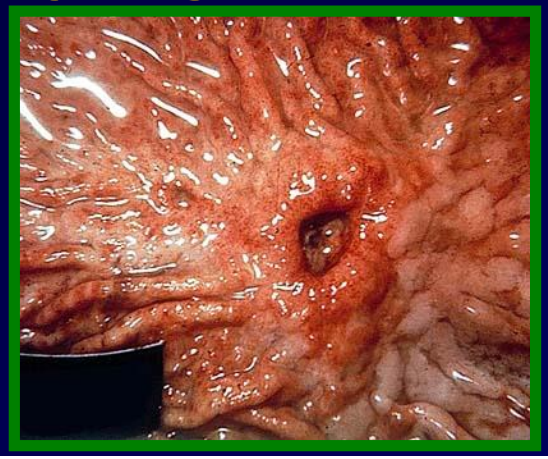
Gastric mucosa -
a sensitive balance of factors preventing self-digestion

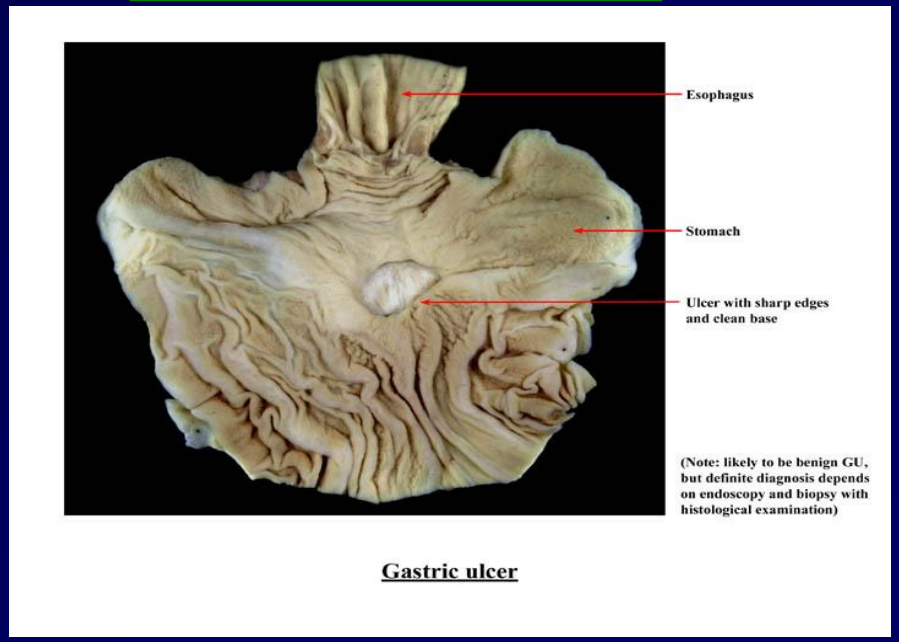
Protective factors
- **bicarbonate**
- **mucus**
- **blood supply**
- **epithelial cell regeneration**

Aggressive factors
- **HCl**
- **pepsin**
- **bile acids**
- **H. pylori**
- **ROS**

Gastric ulcer in antrum of stomach with overlying clot.







Peptic ulcer – *cont.*

H. pylori

Bile reflux

Stress

Prostaglandin synthesis inhibitors

Glucocorticoids

Alcohol

Smoking

Blood flow disturbancy

Regulation of gastric acid secretion

gastric acid is secreted by parietal cells is controled by:

- gastrin ⇧
- histamine ⇧
- acetylcholine ⇧
- prostaglandins E_2, I_2 ⇩

Non-pharmacological therapy

- sleep, stress
- diet /avoid „aggressive“ food, coffeine/
- smoking

Drugs used to treat peptic ulcer

1. Drugs used to diminish effect of HCl

- antisecretory drugs (H_2-blockers, PPI, parasympaticolytics)

- antacids (aluminium hydroxide, magnesium hydroxide, calcium carbonate, sodium bicarbonate)

2. Cytoprotective agents

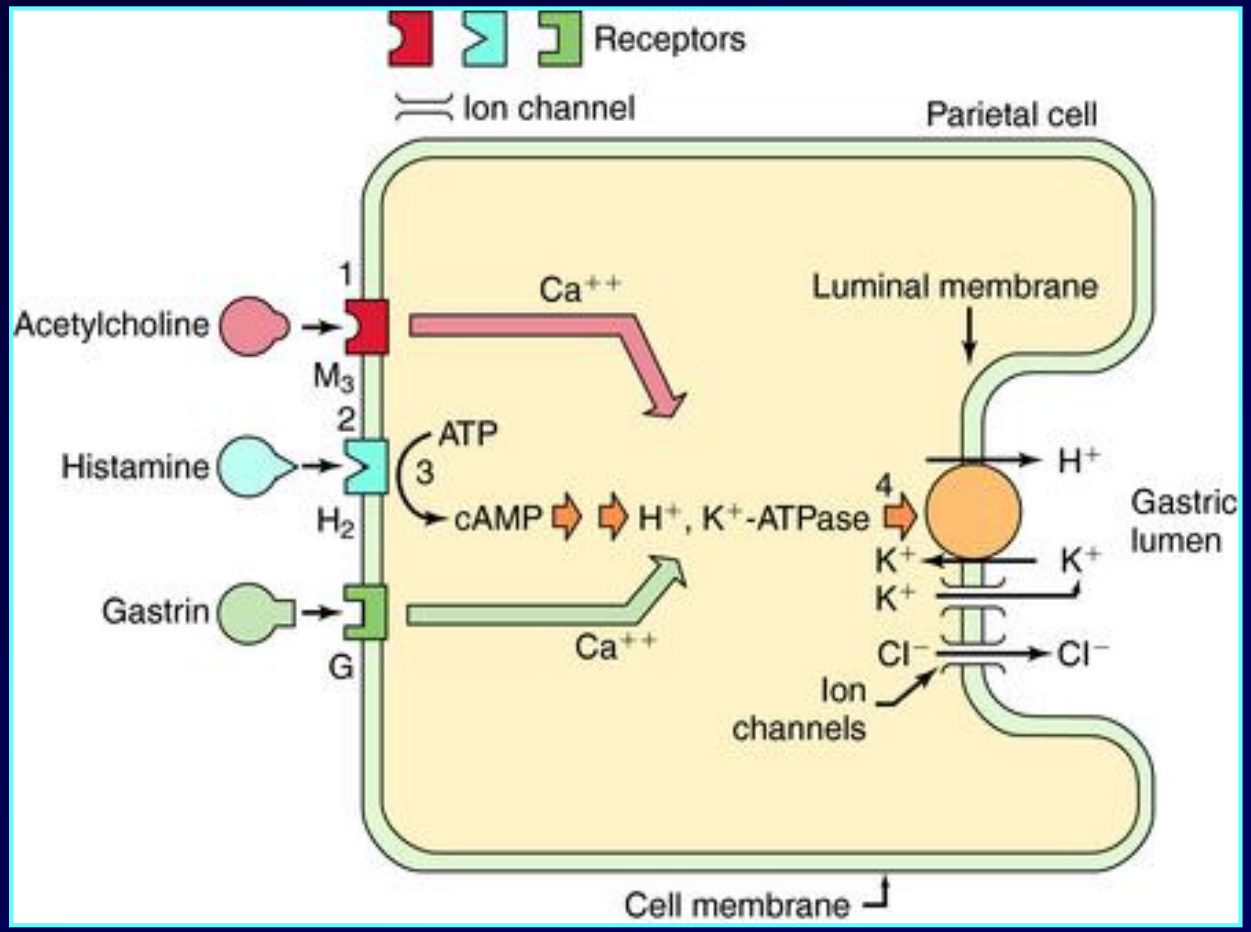
prostaglandins

sucralfate

colloidal bismuth

3. Anti-Helicobacter pylori drugs

Parietal cell



Histamine H_2 receptor blockers

cimetidine, ***ranitidine, nizatidine, famotidine***

- **competetively block the H_2 histamine receptor - decrease basal and food-stimulated acid secretion by 90 % or more**
- **completely inhibit histamine stimulated secretion**
- **partialy inhibit secretion stimulated by gastrin, and acetylcholine**

Pharmacokinetic aspects

- taken orally are well absorbed
- they are distributed widely throughout the body - including breast milk and placenta
- cimetidine has a short serum half-life, blocks cytochrome P_{450}
- ranitidine has longer half-life, 5x more potent than cimetidine, does not inhibit cytochrome P_{450}

- famotidine - similar to rantidine in its action, 20-160x more potent than cimetidine and 3-20x more potent than ranitidine
- nizatidine - similar to ranitidine in action and potency; little first-pass effect - near 100% bioavailability
- ranitidine - oral doses twice daily
- nizatidine and famotidine - once a day

Therapeutic uses

peptic ulcers

- **all agents are equally effective in promoting healing of gastric and duodenal ulcer**

Zollinger-Ellison syndrome

- **rare conditions; gastrin-producing tumor; hypersecretion of gastric acid**
- **however, more effective are PPI**

Acute stres ulcers

- **in patients with acute stress ulcer associated with major physical trauma or great surgery in patients in intensive care units**

***Gastroesophageal reflux disease* (heatburn)**

- **low doses of H_2-antagonist are effective for prevention and treatment of heatburn**
- **they may relieve symptoms for at least 45 minutes**

Unwanted effects

- are usually minor
- diarrhoea, dizziness, muscle pain

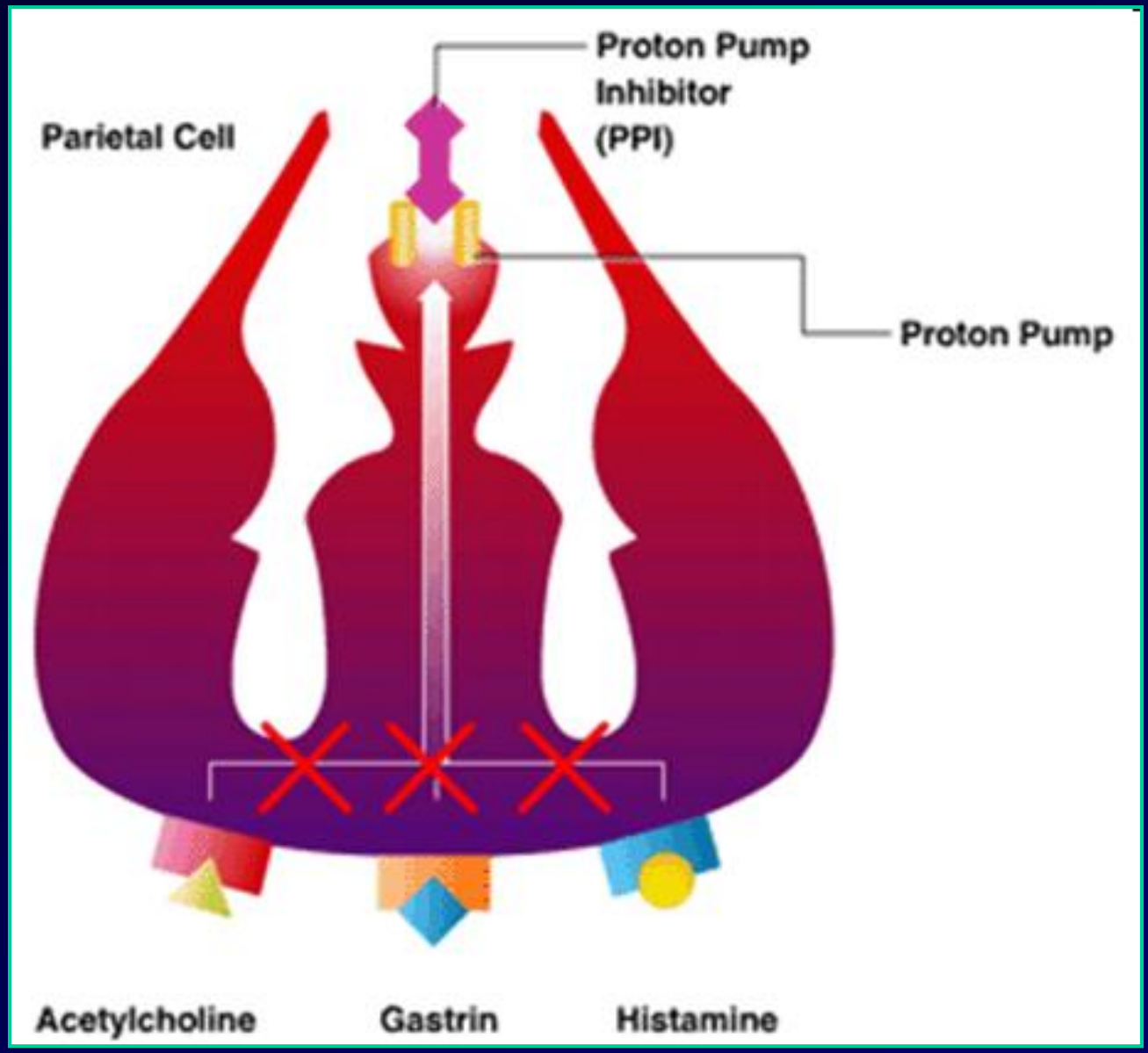
- cimetidine: gynecomastia in men, decrease in sexual function, inhibition of cytochrome P-450

- ranitidine has lower affinity to the androgen receptors and cytochrome P-450
- H_2-antagonists appear to be safe drugs

Proton-pump inhibitors (PPI)

omeprazole, lansoprazole, pantoprazole …

- **they block (irreversible) H^+/K^+-ATPase - the final step in the acid secretory pathway**
- **inhibit basal and stimulated acid secretion more than 90%**
- **acid suppression begins within 1-2 hours with lansoprazole and slightly erlier with omeprazole**
- **they are inactive at neutral pH and they are activated at pH lower than 3**

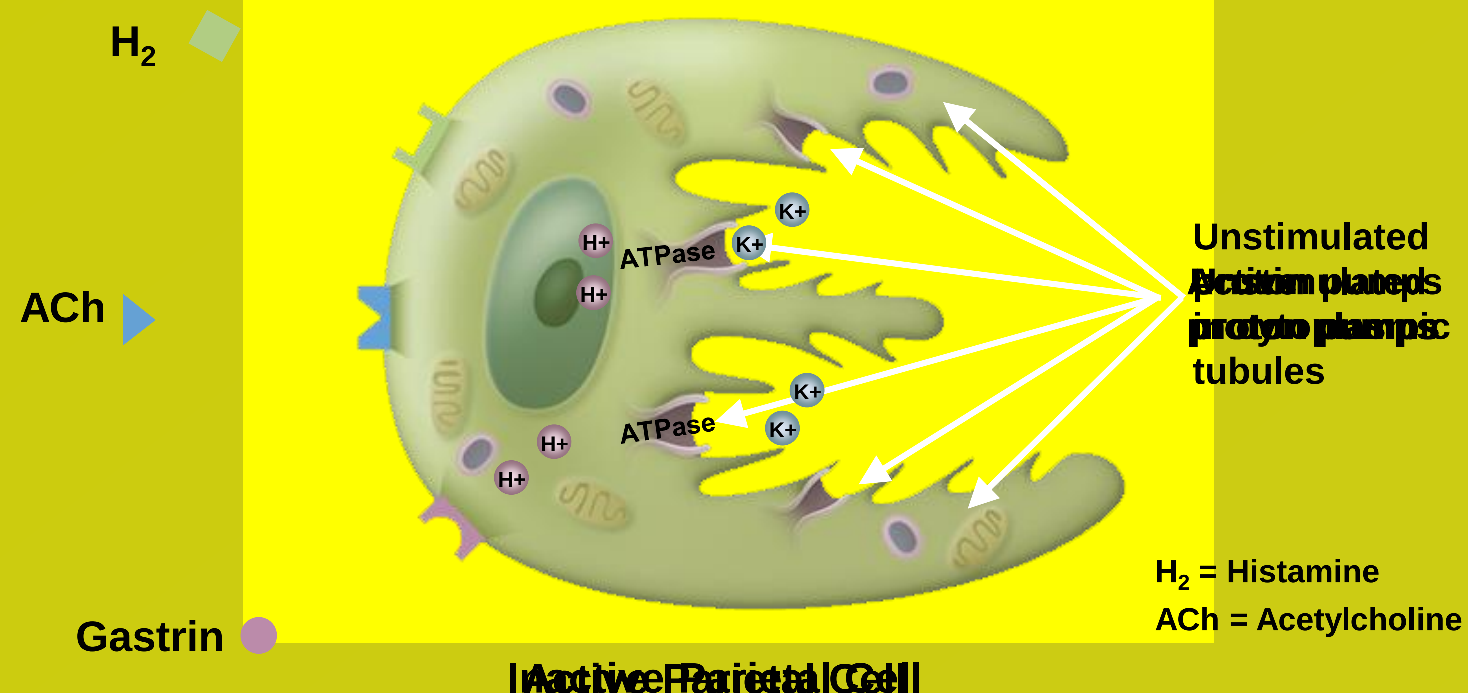

Proton Pump
Inhibitor
(PPI)
Parietal Cell
Proton Pump
Acetylcholine
Gastrin
Histamine

PPI: Mechanism of Action

- PPI are activated in the acidic compartments of parietal cells
- THUS, they only inhibit actively secreting proton pumps

Proton Pump Functioning

After activation, the parietal cell undergoes structural changes, allowing proton pumps to reach the surface of the parietal cell[1]

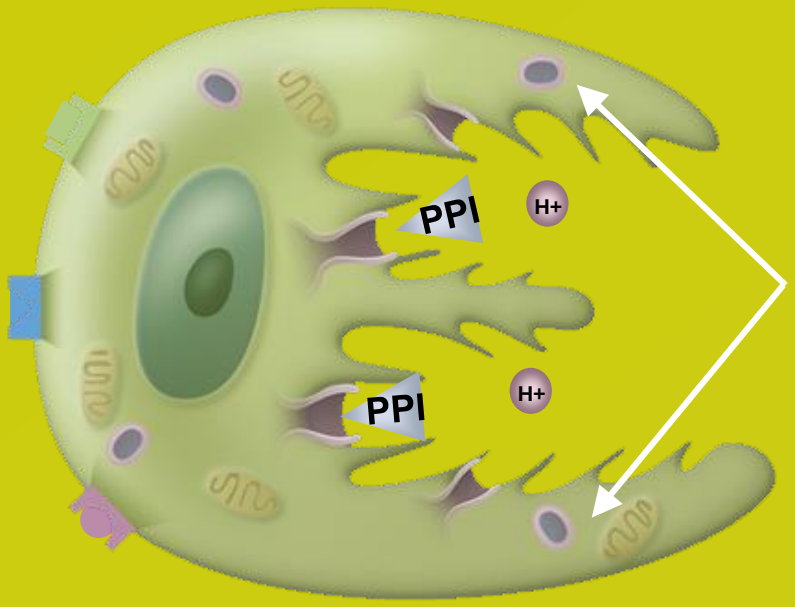


1. Del Valle J, et al. In: Yamada et al, eds. *Textbook of Gastroenterology*. 4th ed. Philadelphia, Pa: Lippincott Williams and Wilkins; 2003:1321-1376.
2. Sachs G. *Pharmacotherapy*. 1997;17:22-37.

Proton Pump Inhibitors

Acid is required to convert a PPI into its active form[1]

PPI only bind to active proton pumps



Unstimulated proton pumps remain

1. Del Valle J, et al. Acid peptic disorders. In: Yamada et al, eds. *Textbook of Gastroenterology*. 4th ed. Philadelphia, Pa: Lippincott Williams and Wilkins; 2003:1321-1376.

Pharmacokinetic aspects

- given orally are well absorbed
- they are enteric-coated pills to protect them from premature activation
- after absorption in duodenum - transport to the parietal cells
- single daily dose affects acid secretion about 2-3 days
- they are rapidly and completly eliminated by biotransformation to inactive products
- metabolites are excreted in urine and feces

Therapeutic uses

- proton-pump blockers are useful in patient resistant to other types of antisecretory drugs

Zollinger-Ellison syndrome

- they are extremly valuable in patients with Zollinger-Ellison syndrome

Erosive esophagitis

- used for short-term therapy
- ***Peptic ulcer and gastroesophageal reflux***
- use in peptic ulcer - healing of 90-100% patients after 4 weeks therapy

Unwanted effects

- headache, diarrhea & abdominal pain.
- achlorhydria
- hypergastrinaemia.
- gastric mucosal hyperplasia
  - increased bacterial flora
  - increased risk of community-acquired respiratory infections & nosocomial pneumonia

Long term use:

- Vitamin B_{12} deficiency

Muscarinic-receptor antagonists

pirenzepine, telenzepine - main parasympatholytic antisecretory drugs

- the main effects of parasympathetic stimulation - increase in motility and secretion activity
- muscarinic M1 receptor blockade
- telenzepine - anti-secretory effect 4-10 x ⇧

M-receptor antagonists – *cont.*

- all are given orally
- therapeutic doses - inhibitory effect at other M-receptors - unwanted effects
- pirenzepine shows a greater specificity
- about 20% of patients - dry mouth and blurred vision
- telenzepine – 3-10x more potent than prirenzepine

Antacids

- weak bases that neutralize gastric acid
- they do not decrease acid secretion
- neutralisation of gatric acid results in two therapeutic effects:
  - decrease in total acid delivered to the duodenum
  - inhibition of pepsin activity
- less effective than H_2-blockers or PPI

Antacids – *cont.*

a) systemic - are higly soluble and are rapid absorbed from the gut

sodium bicarbonate

- **act rapidly - ⇧ gastric pH to about 7.4**
- **carbon dioxide is liberated - belching**
- **CO_2 stimulates gastrin release - secondary rise in acid secretion**
- **can be absorbed in intestine and ⇧ blood pH (metabolic alkalosis) and alkalinize urine**
- **sodium bicarbonate should not be prescribed for the long-term therapy of peptic ulcer**

Antacids – *cont.*

b) non-systemic - are less soluble and exert their antacid action locally in the GIT

- they are preferred because of safety and longer duration of action
- non-systemic antacids usually contain calcium, aluminium or magnesium ions

Antacids – *cont.*

aluminium hydroxide - **neutralises HCl forming insoluble aluminium chloride and water**

- **⇧ the gastric juice pH to about 4**
- **it also absorb pepsin**
- **long-continued use can cause constipation**
- **it binds to phosphate - it may lead to phosphorus deficiency**
- **in patients with renal failure - cumulation of aluminium - toxic effects ?**

Antacids – *cont.*

- ***magnesium hydroxide*** **- neutralises gastric acid forming insoluble magnesium chloride**
- **some unchanged drug passes into duodenum - diarrhea**
- **many antacids combine both aluminium and magnesium hydroxides to prevent diarrhea (caused by magnesium) and obstipation (caused by aluminium ions)**
- **rapid onset of action**

- ***calcium carbonate*** **- relatively rapid onset of action - calcium chloride**
- **pH is usually raised to only 4-5**
- **about 10 % of $CaCl_2$ is absorbed - hypercalcemia**

- **calcium ions can stimulate acid secretion, resulting in „acid rebound“**

Mucosal protective agents

- protection of gastric mucosa by:

  formation a barrier over the gastric surface

  stimulation of bicarbonate secretion

  both

Prostaglandins

- antisecretory and cytoprotective actions on the gastric and duodenal mucosa
- in parietal cells inhibit adenylyl cyclase stimulation by histamine - inhibition of essential step in histamine-stimulated acid secretion
- they are more effective in reducing NSAIDs-induced mucosal damage than cimetidine
- *misoprostol* - a synthetic analogue of PGE_2 - causes ulcer healig - comparable with cimetidine effectivity

Sucralfate

- complex of aluminium hydroxide and sulphated sucrose
- selectively binds to necrotic ulcer tissue
- it acts as a barrier to HCl and pepsine and is effective in ulcer healing
- it also stimulates production:
  - mucus
  - bicarbonate
  - prostaglandine

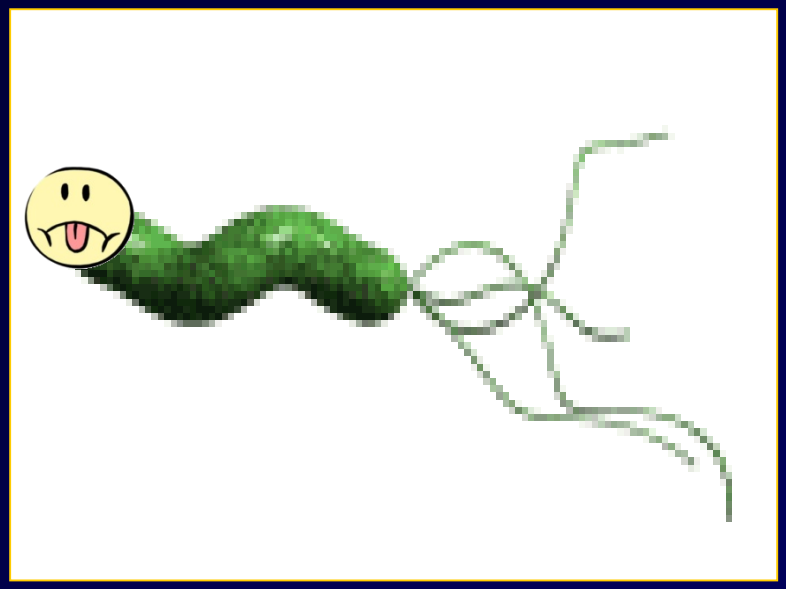
Sucralfate – *cont.*

- it requires an acidic pH for activation - it should not be administered with antacids
- it is administerd orally, 4 times daily before meals
- about 30 % is present in the stomach 3 hours after administration
- only small amount is absorbed systemicaly
- unwanted effects are rare - obstipation

Colloidal bismuth

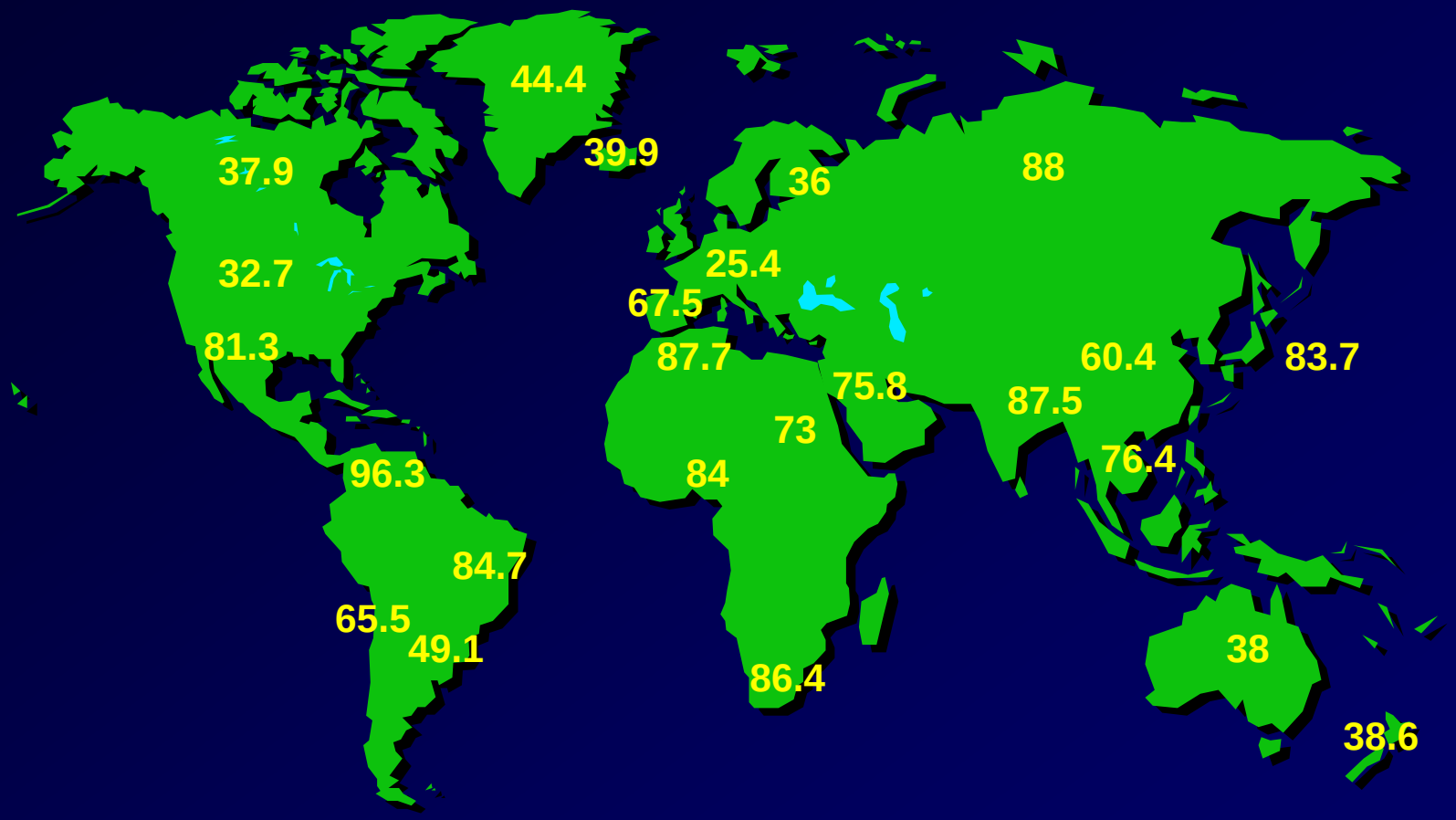
- it may act by coating of ulcer and protecting it
- it is also bactericidal against *Helicobacter pylori*
- *H. pylori* - has been implicated in the pathogenesis of peptic and particularly duodenal ulcer
- erradication - significantly lowers the relapse rate
- colloidal bismuth causes darkening of the faeces and stains tongue and teeth black
- it should not be used in severe renal failure - encephalopathy

Helicobacter pylori



- Gram negative bacterium
- Spiral shaped
- Colonizes human stomach
- High prevalence
- Associated with gastritis, peptic ulcer and gastric cancer

World Prevalence



Percent of the Population Infected with *H. pylori*

Helicobacter pylori

- ***H.pylori*** **- discovered by Marshall and Warren at 1983**

- **2005 – Nobel Prize (Medicine and Physiology)**

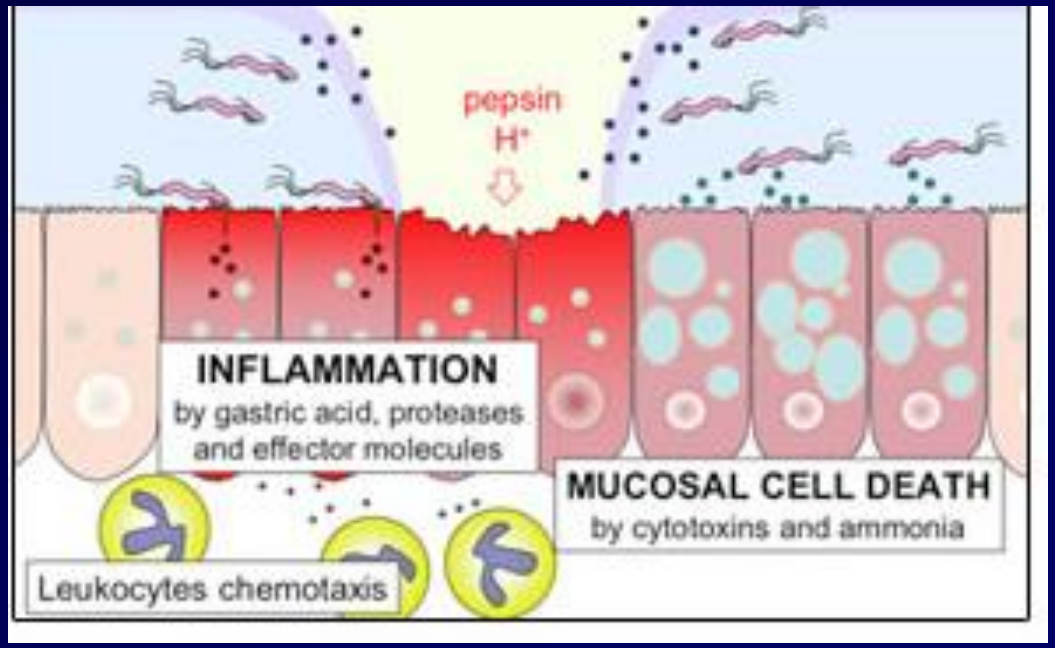
H. pylori-positive ulcers

Mechanisms of gastric mucosa injury in HP+

- **decrease of mucus production**
- **amonia production**
- **liposacharides of HP - stimulation of HCl and pepsin secretion**
- **ROS**
- **phagocytes**

H. pylori

- Secret proteins and toxins that interact with the stomach's epithelial cells
- Leads to inflammation and damage



Treatment

- Goal of treatment to eradicate infection

- **Triple therapy regimens** consist of one anti-secretory agent and two antimicrobial agents for 10 to 14 days

- Triple therapy regimens must
  - have cure rate of approximately 80%
  - be without major side effects
  - minimal induction of resistance

Drugs used for HP erradication

- **Antibiotics:** metronidazole, tetracycline, clarithromycin, amoxicillin
- **Proton pump inhibitors:** omeprazole, lansoprazole
- **Stomach-lining protector:** bismuth subsalicylate