Drugs of the Respiratory System

Pharmacology Team

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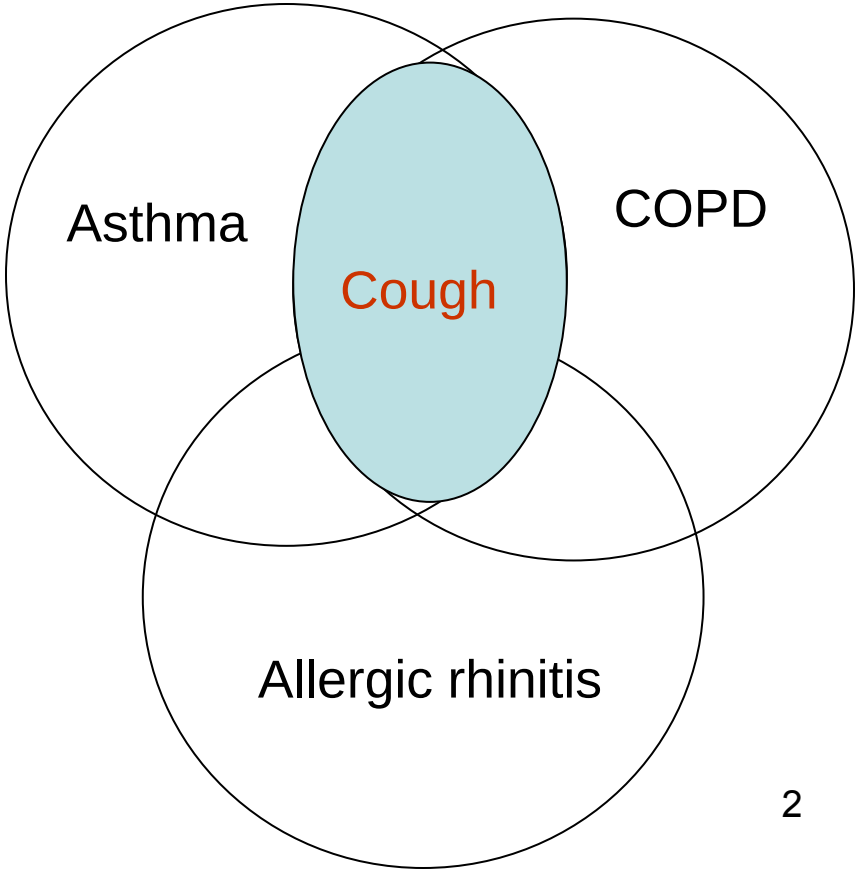
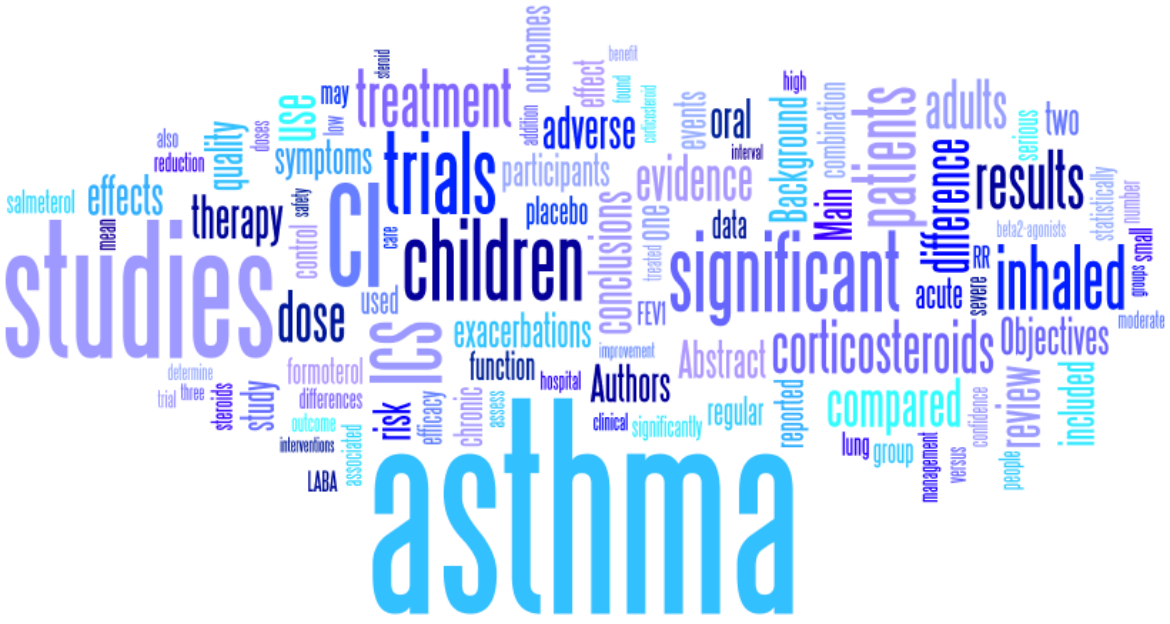
Overview

- **Common respiratory diseases:**
  1. Asthma
  2. Chronic obstructive pulmonary disease (COPD)
  3. Allergic rhinitis.



Respiratory Disorders

- **Asthma:** is a chronic disease characterized by hyperresponsive airways
- **COPD:** (emphysema or chronic bronchitis)
- **Allergic rhinitis**, characterized by:
  - itchy, watery eyes
  - runny nose
  - nonproductive cough
- **Coughing**: defensive respiratory response t


asthma
studies
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Objectives
Abstract
Authors
Background
Main
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adults
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interval
combination
events
serious
statistically
number
small
groups
moderate
beta2-agonists
improvement
treated
one

Clinical features of bronchial asthma

1. Acute attacks of dyspnea associated with acute airway obstruction due to **contraction of airway smooth muscle**

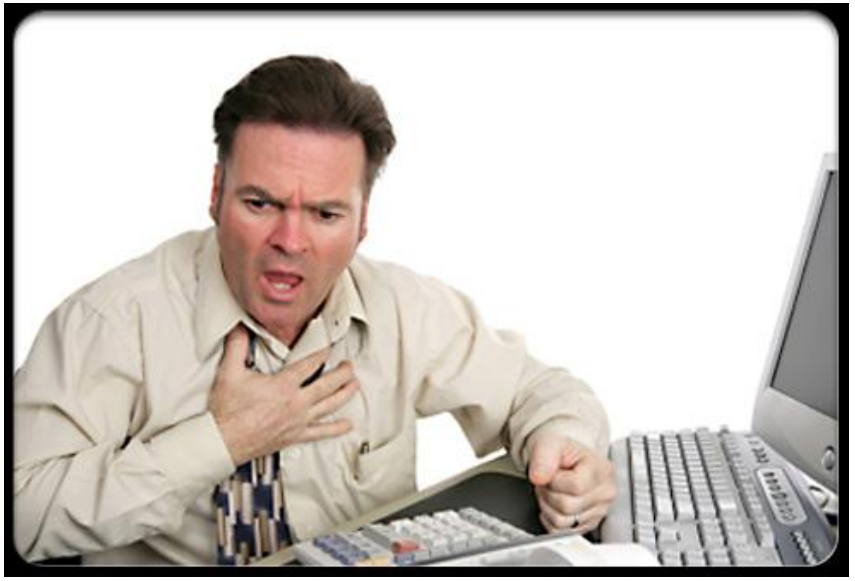
2. **Mucus hypersecretion**: May lead to mucus plugging

3. **Airway inflammation**

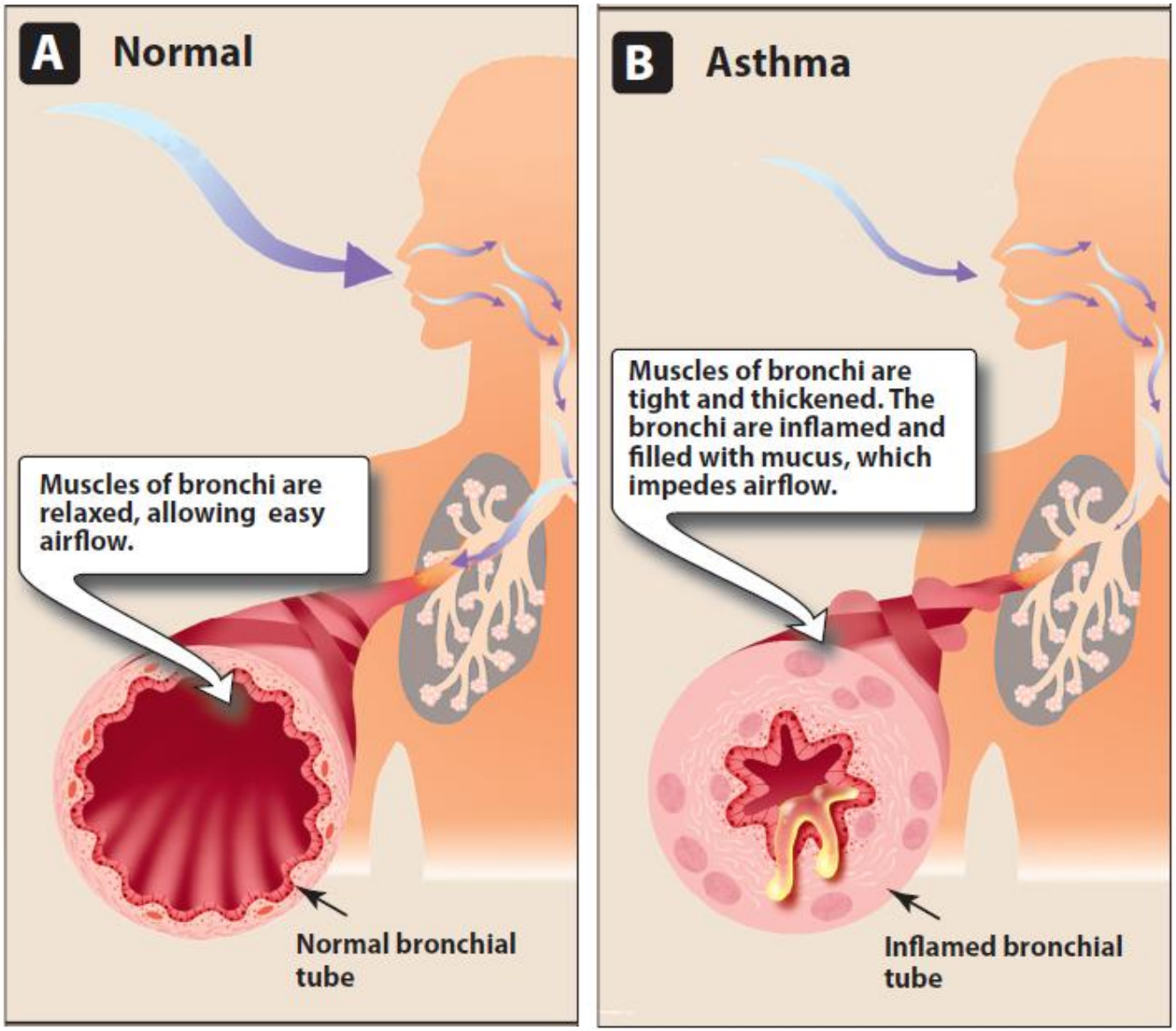
4. **Bronchial hyper-responsiveness**

Bronchial asthma is associated with

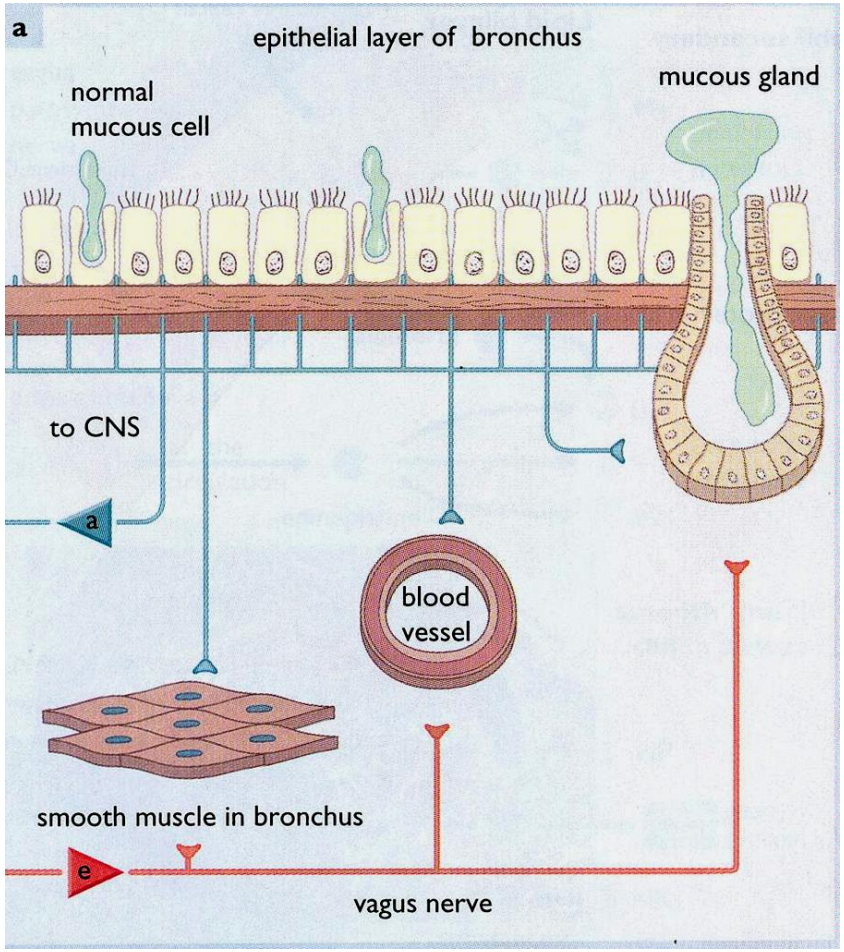
- ✓ Shortness of breath
- ✓ Cough
- ✓ Chest tightness
- ✓ Wheezing
- ✓ Rapid respiration



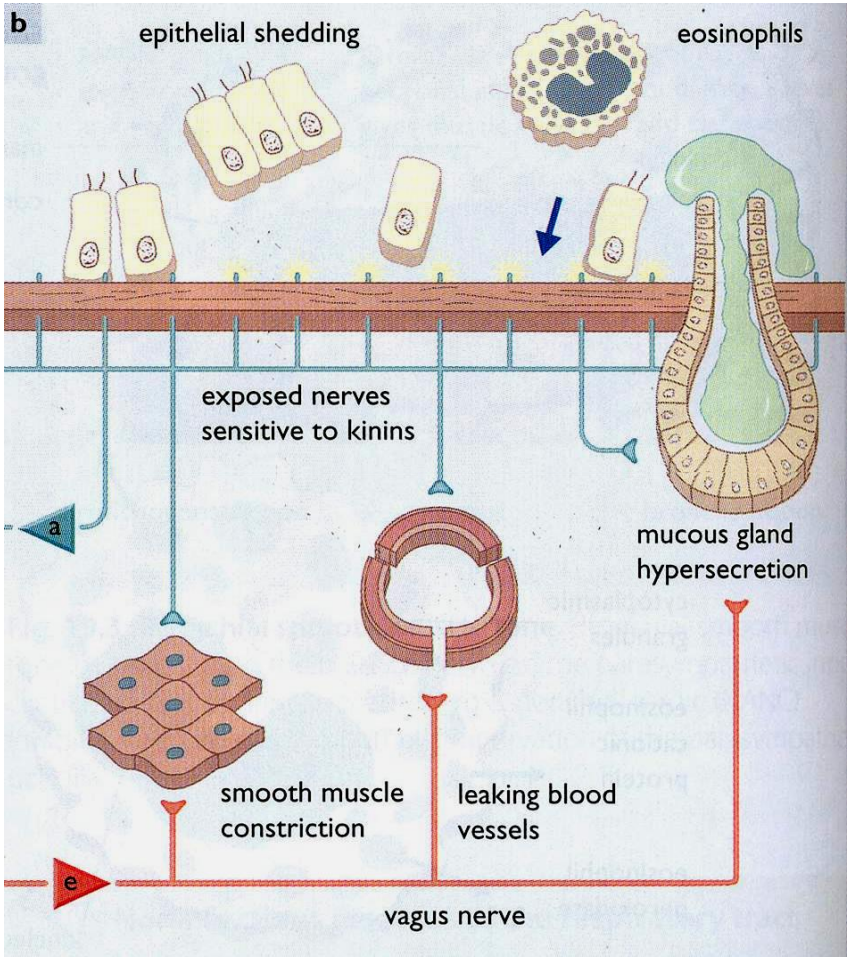
Clinical features of bronchial asthma



Mechanism of bronchial hyperresponsiveness



Normal lung



Asthmatic lung

Types and triggers of bronchial asthma

- Allergens
- Respiratory infections
- Chemical irritants
- Dust, smokes
- Cold
- Post-exercise
- Psychogenic
- Post-coughing
- Post-hyperinflation
- Post-laughter

These acute symptoms may resolve:

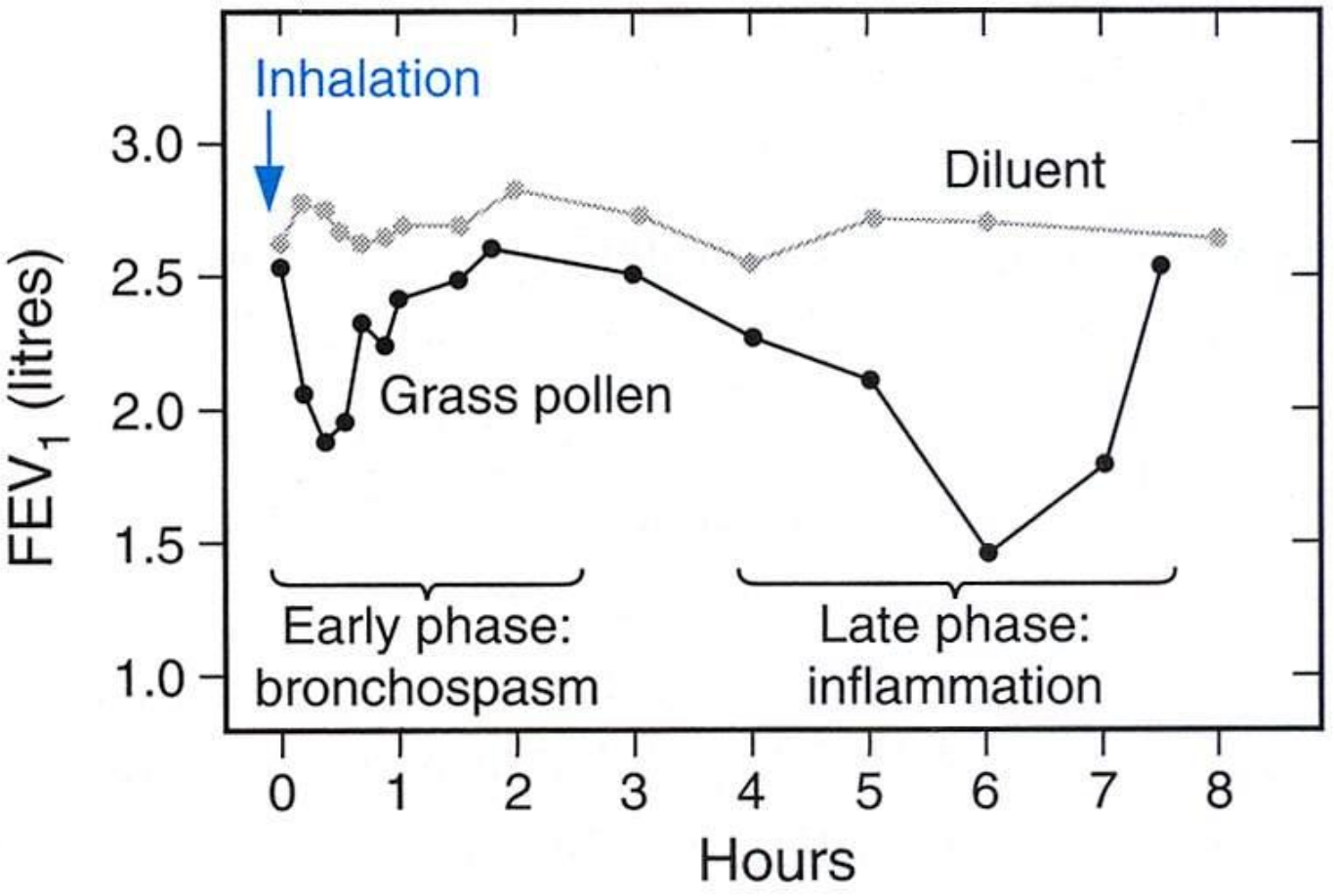
- Spontaneously
- With nonpharmacologic relaxation exercises, or
- With use of “quick relief” medications, such as a short-acting β2-adrenergic agonist

Types and triggers of bronchial asthma

- Unlike COPD, cystic fibrosis, and bronchiectasis, asthma is usually not a progressive disease (does not inevitably lead to incapacitated airways).

- However, if untreated, asthma may cause airway remodeling, resulting in increased severity and incidence of asthma exacerbations and/or death.

The two phases of asthma



FEV_1: forced expiratory volume in 1 second

Pharmacology of Asthma

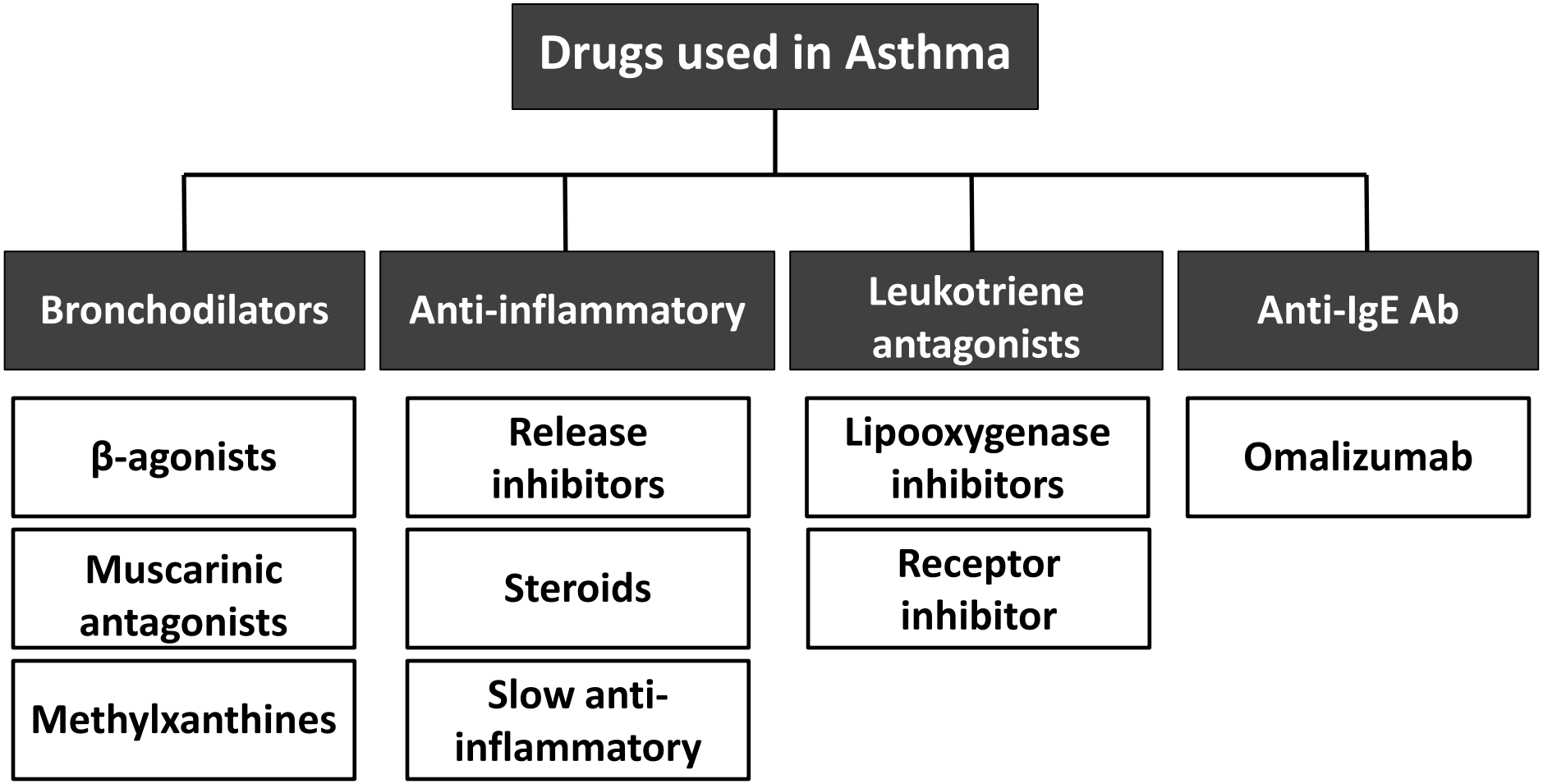
Goals of therapy

- To decrease the intensity and frequency and severity of asthma symptoms
- All patients need to have a “quick-relief” medication to treat acute asthma symptoms.
- Drug therapy for long-term control of asthma is designed to reverse and prevent airway inflammation.

- **Drugs used to treat respiratory conditions can be delivered:**

  - ✓ Topically to the nasal mucosa: nasal sprays
  - ✓ Inhaled into the lungs: inhalers
  - ✓ Orally or parenterally.

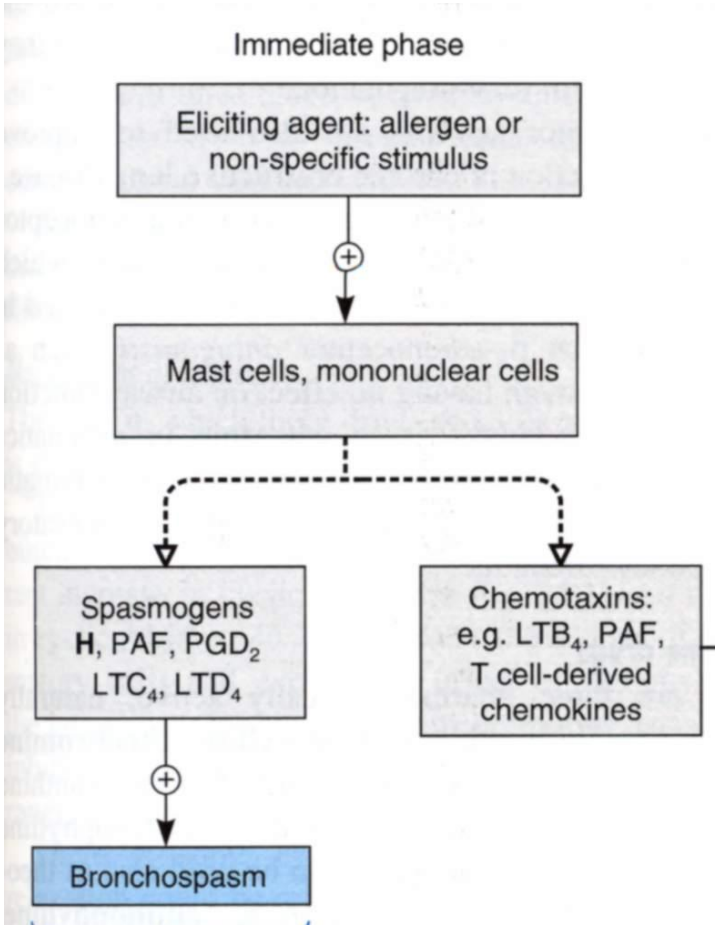
- **Clinically useful drugs alleviate the specific pathology by:**
  - ✓ Relaxing bronchial smooth muscle or
  - ✓ Modulating the inflammatory response.

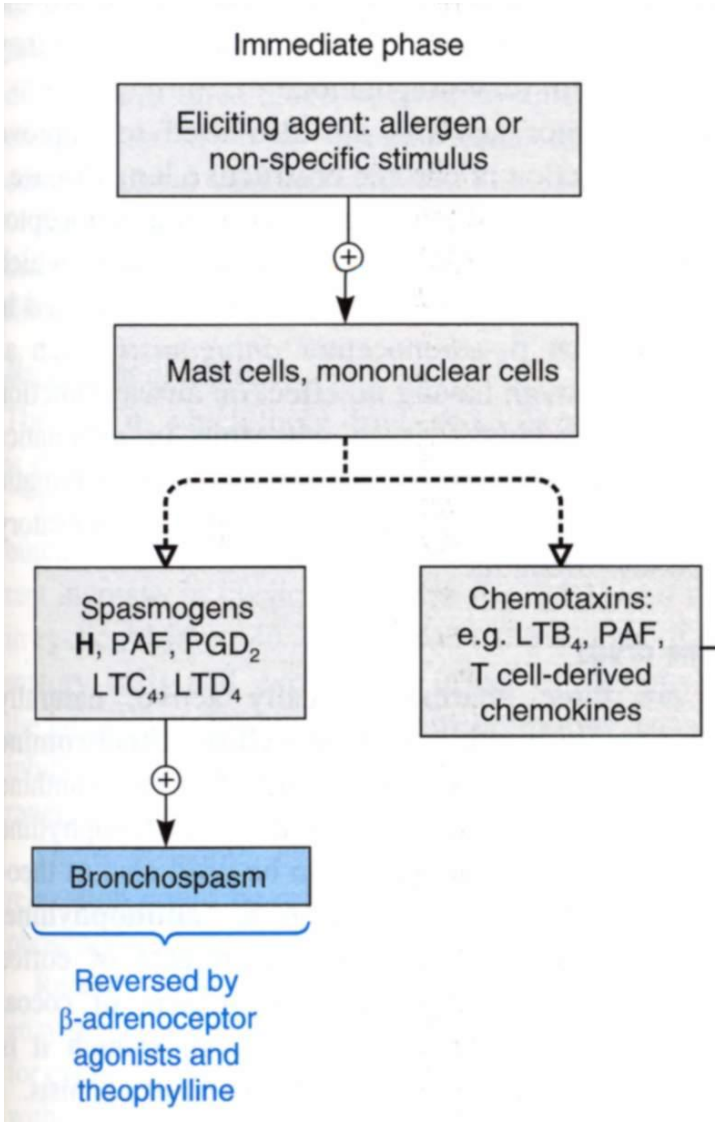

Drugs used in Asthma
Bronchodilators
Anti-inflammatory
Leukotriene antagonists
Anti-IgE Ab
β-agonists
Muscarinic antagonists
Methylxanthines
Release inhibitors
Steroids
Slow anti-inflammatory
Lipooxygenase inhibitors
Receptor inhibitor
Omalizumab

Guidelines for the treatment of asthma

CLASSIFICATION	BRONCHO-CONSTRICTIVE EPISODES	RESULTS OF PEAK FLOW OR SPIROMETRY	LONG-TERM CONTROL	QUICK RELIEF OF SYMPTOMS
Intermittent	Less than 2 days per week	Near normal*	No daily medication	Short-acting β_2 agonist
Mild persistent	More than 2 days per week, not daily	Near normal*	Low-dose ICS	Short-acting β_2 agonist
Moderate persistent	Daily	60% to 80% of normal	Low-dose ICS + LABA OR Medium-dose ICS	Short-acting β_2 agonist
Severe persistent	Continual	Less than 60% of normal	Medium-dose ICS + LABA OR High-dose ICS + LABA	Short-acting β_2 agonist

ICS = inhaled corticosteroid. LABA = long-acting β_2 agonist.


Immediate phase
Eliciting agent: allergen or non-specific stimulus
Mast cells, mononuclear cells
Spasmogens
H, PAF, PGD_2
LTC_4, LTD_4
Chemotaxins:
e.g. LTB_4, PAF,
T cell-derived
chemokines
Bronchospasm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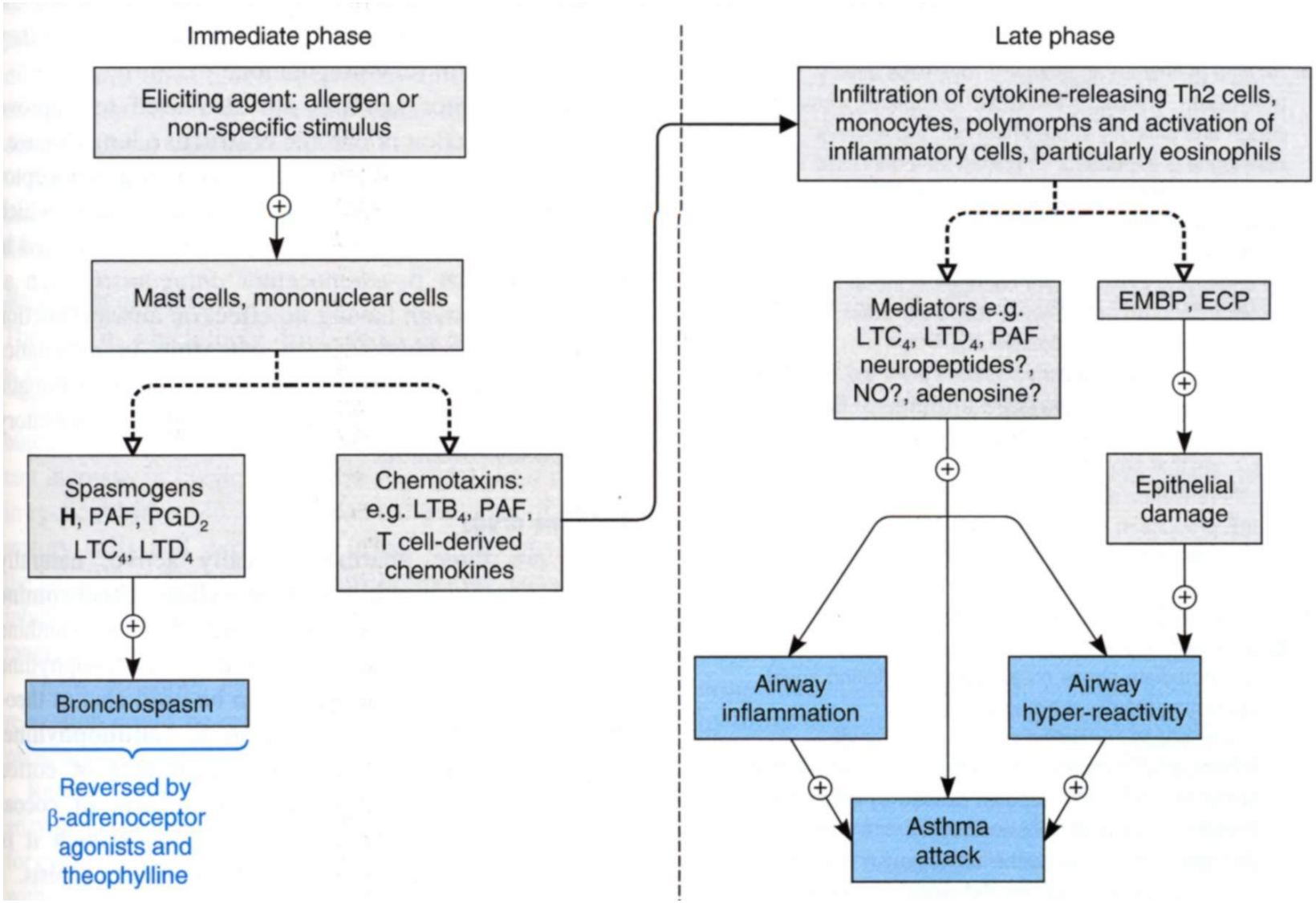
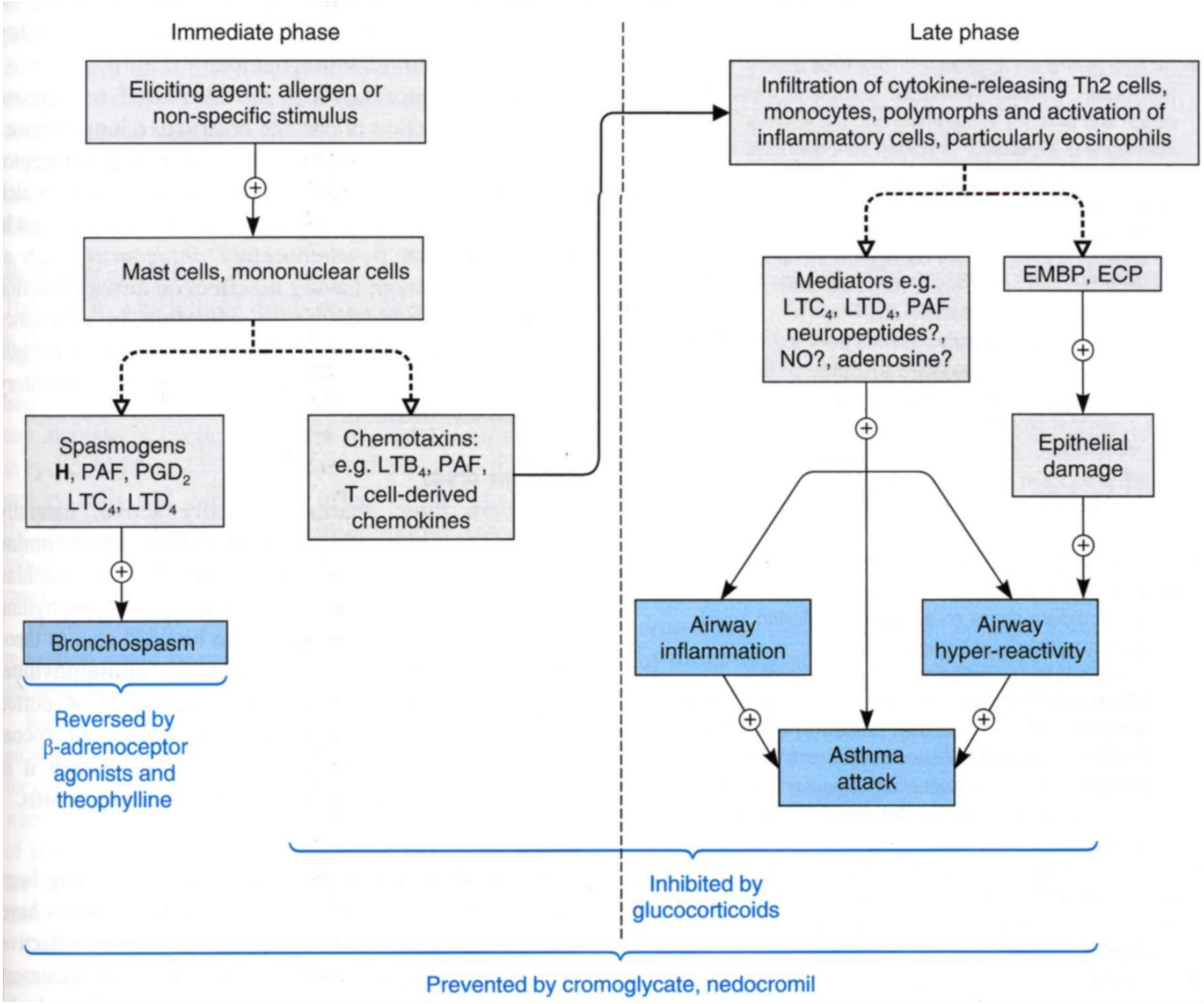
Bronchospasm
Reversed by
β-adrenoceptor
agonists and
theophylline


Immediate phase
Late phase
Eliciting agent: allergen or non-specific stimulus
Mast cells, mononuclear cells
Spasmogens H, PAF, PGD_2 LTC_4, LTD_4
Chemotaxins: e.g. LTB_4, PAF, T cell-derived chemokines
Bronchospasm
Reversed by β-adrenoceptor agonists and theophylline
Infiltration of cytokine-releasing Th2 cells, monocytes, polymorphs and activation of inflammatory cells, particularly eosinophils
Mediators e.g. LTC_4, LTD_4, PAF neuropeptides?, NO?, adenosine?
EMBP, ECP
Epithelial damage
Airway inflammation
Airway hyper-reactivity
Asthma attack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EMBP, ECP
Epithelial damage
Airway inflammation
Airway hyper-reactivity
Asthma attack
Inhibited by glucocorticoids
Prevented by cromoglycate, nedocromil

1. β receptor agonists

- Inhaled β2-adrenergic agonists directly relax airway smooth muscle.

- They are used for the quick relief of asthma symptoms and as adjunctive therapy for long-term control of the disease

1. β receptor agonists

Mechanism of Action:

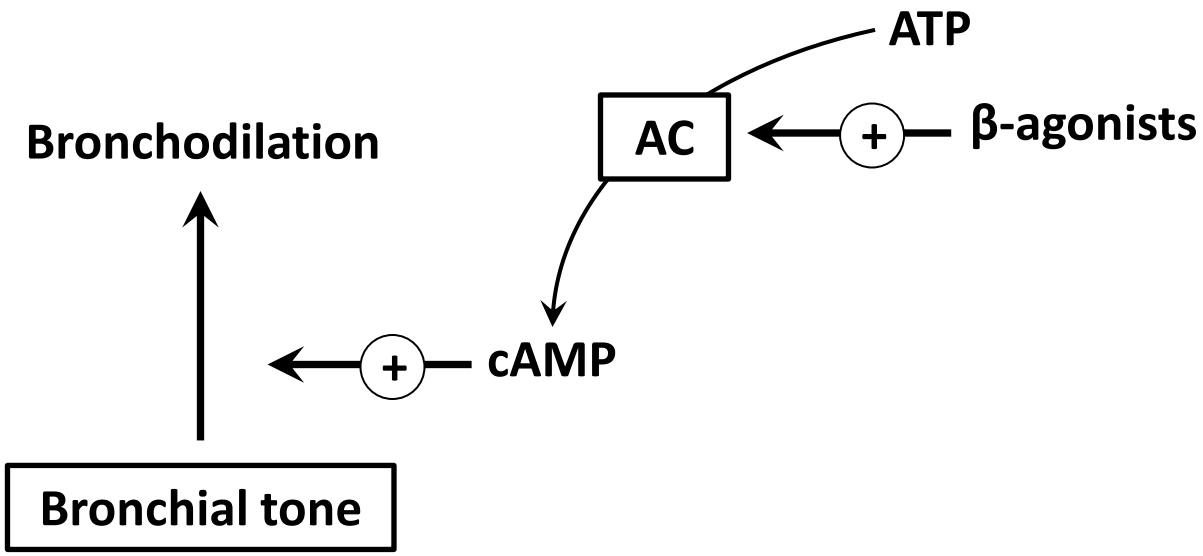
a. β1 receptor

- increases heart rate
- increases contractile force

b. β2 receptor

- relaxes bronchial smooth muscle
- relaxes vascular smooth muscle
- relaxes uterine smooth muscle

Bronchodilation is promoted by cAMP



β2 receptor agonists

A. **Quick therapy:** Short-acting β2 agonists (SABAs)

- **Direct-acting selective β2- agonists:** Terbutaline, Albuterol (Salbutamol).
- **Rapid onset of action:** 5–30 min
- **Duration:** 4 to 6 hours.
- Used for symptomatic treatment of bronchospasm: quick relief of acute bronchoconstriction.

- All patients with asthma should be prescribed a SABA inhaler

β2 receptor agonists

A. **Quick therapy:** Short-acting β2 agonists (SABAs)

- β2 agonists have no anti-inflammatory effects, and they should never be used as the sole therapeutic agents for patients with persistent asthma.

- Monotherapy with SABAs may be appropriate for patients with intermittent asthma or exercise-induced bronchospasm

β2 receptor agonists

B. Long term control: long-acting β2 agonists (LABAs)

- **Drugs:** Salmeterol and Formoterol
- **Long duration of action**: at least 12 hours.
- **Onsets of action:** Slow
- Should not be used for quick relief of an acute asthma attack.

β2 receptor agonists

- The use of LABA as monotherapy is contraindicated
- LABAs should be used only in combination with an asthma controller medication.
- Inhaled corticosteroids (ICS) remain the long-term controllers of choice in asthma, and LABAs are considered to be useful adjunctive therapy.
- Some LABAs are available as a combination product with an ICS

Side effects of β2 receptor agonists

- Tachycardia
- Hyperglycemia
- Hypokalemia & hypomagnesemia
- β2-mediated skeletal muscle tremors

These side effects are minimized with inhaled dosage forms

Corticosteroids

- ICS are the drugs of choice for long-term control in patients with any degree of persistent asthma.

- Corticosteroids inhibit the release of arachidonic acid through phospholipase A2 inhibition thereby producing direct anti-inflammatory properties in the airways

Corticosteroids

- Inhaled corticosteroids (ICS) are the drugs of first choice of persistent asthma (mild, moderate, or severe).
- Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment.
- No other medications are as effective as ICS in the long-term control of asthma in children and adults
- To be effective in controlling inflammation, glucocorticoids must be taken continuously.

Actions of Corticosteroids on lung

- ICS do not directly affect the airway smooth muscle.

- **ICS therapy directly targets underlying airway inflammation by:**
  - Decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes)
  - Reversing mucosal edema
  - Decreasing the permeability of capillaries
  - Inhibiting the release of leukotrienes.

Actions of Corticosteroids on lung

- After several months of regular use, ICS **reduce the hyperresponsiveness** of the airway smooth muscle to a variety of bronchoconstrictor stimuli, such as allergens, irritants, cold air, and exercise

Route of administration of CS

a. **Inhalation: “Metered-dose inhalers “ (MDI) and “Dry powder inhalers “ (DPI)**

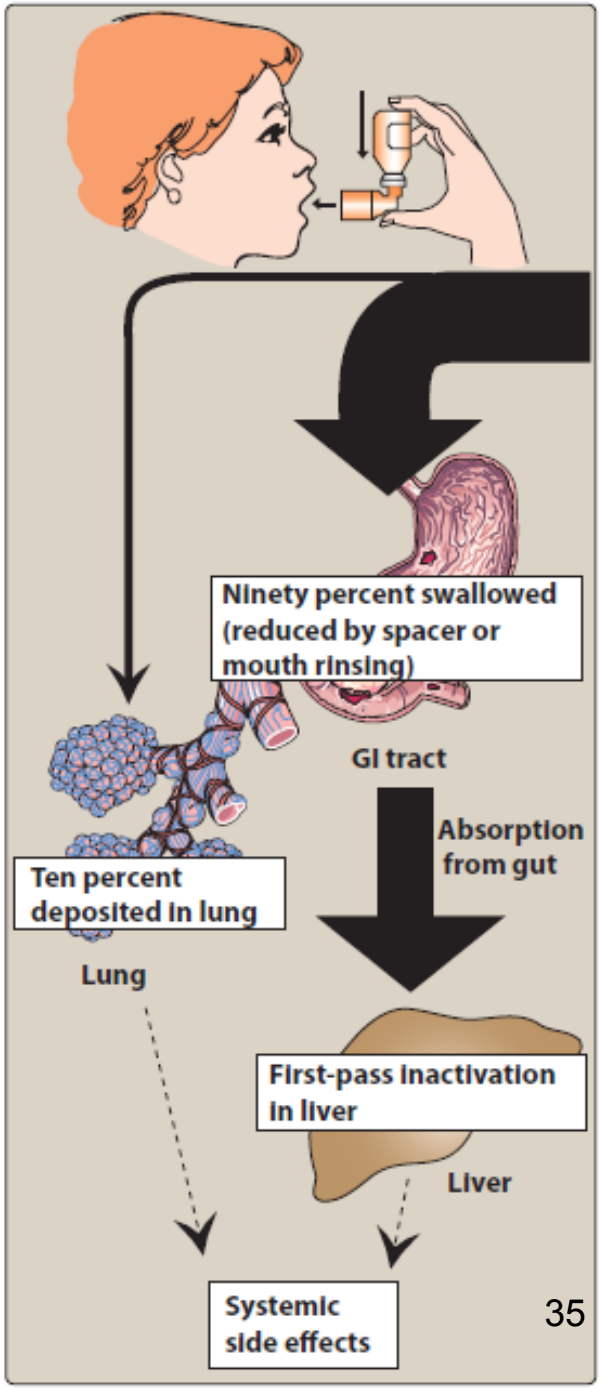
- **MDI** have **propellants** that eject the active medication from the canister.

- Patients should be instructed to **SLOWLY** and **DEEPLY** inhale upon activation of these inhalers to avoid impaction of the medication onto the laryngeal mucosa rather than the bronchial smooth muscle.

- Improper use of a metered-dose inhaler can result in a large fraction (typically 80–90 percent) of inhaled glucocorticoids to be deposited in the mouth, pharynx, and/or swallowed.

- The 10 - 20 % of the metered dose of inhaled glucocorticoids that is not swallowed is deposited in the airway.

- If ICS are inappropriately inhaled, systemic absorption and adverse effects are much more likely.



Inhalation by "Dry powder inhalers " (DPI): Requires a different inhaler technique.

- Patients should be instructed to inhale **QUICKLY** and **DEEPLY** to optimize drug delivery to the lungs.

Inhalation by "Dry powder inhalers " (DPI): Requires a different inhaler technique.

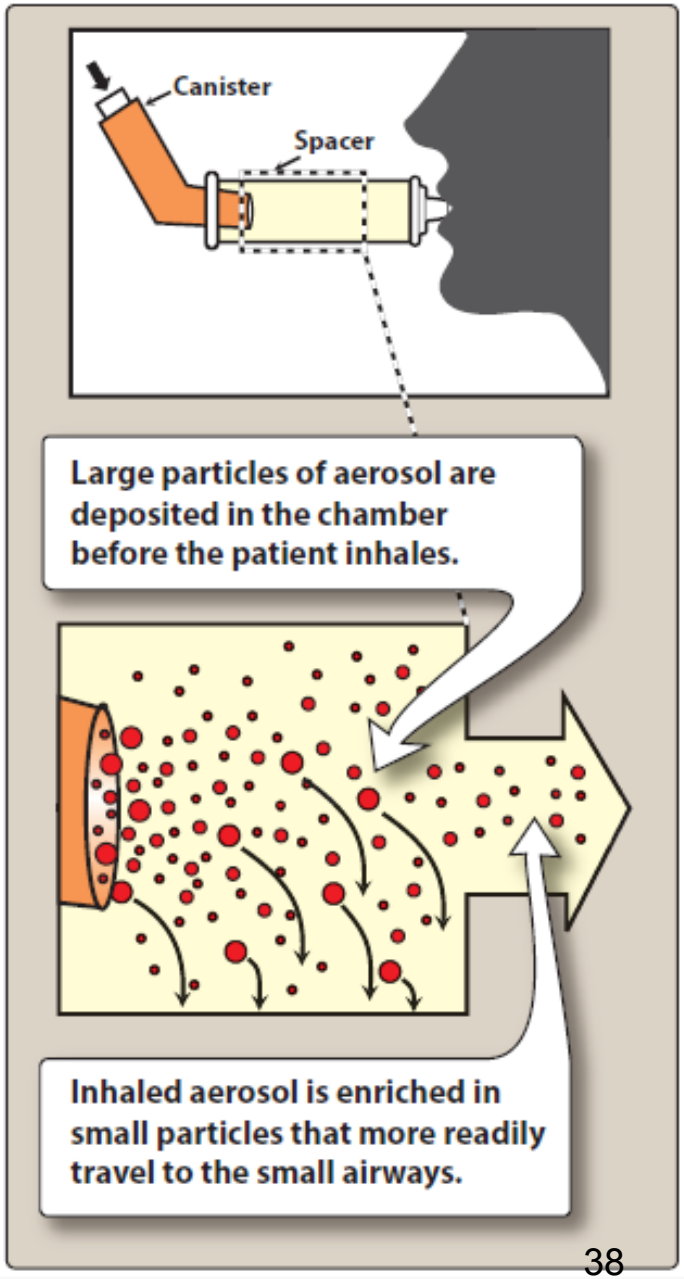
- Patients should be instructed to inhale **QUICKLY** and **DEEPLY** to optimize drug delivery to the lungs.

- **Corticosteroid deposition on the oral and laryngeal mucosa can cause adverse effects such as**
  - Oropharyngeal candidiasis
  - Hoarseness

- Patient counseling incorporating a rinsing of these tissues via the "swish and spit" method should avoid these adverse events.

Spacers:

- A spacer is a large-volume chamber attached to a metered-dose inhaler.
- Spacers decrease the deposition of drug in the mouth caused by improper inhaler technique.
- The smaller, higher-velocity drug particles are less likely to be deposited in the mouth and more likely to reach the target airway tissue.



b. Oral/systemic:

- Patients with severe exacerbation of asthma (status asthmaticus) require intravenous methylprednisolone or oral prednisone to reduce airway inflammation.

- In most cases, suppression of the hypothalamic–pituitary–adrenal cortex axis will not occur during the short course of oral prednisone "burst" typically prescribed for an asthma exacerbation

- Prednisone dose taper is unnecessary prior to discontinuation

- Due to the increased incidence of adverse effects with oral therapy, chronic maintenance with systemic administration of corticosteroids should be reserved for patients who are not controlled on an ICS.

Adverse effects

- Oral or parenteral glucocorticoids have a variety of potentially serious side effects
- ICS, particularly if used with a spacer, have few systemic effects.
- ICS deposition on the oral and laryngeal mucosa can cause adverse effects: oropharyngeal candidiasis (due to local immune suppression) and hoarseness.
- Patients should be instructed to rinse the mouth in a “swish-and-spit” method with water following use of the inhaler to decrease the chance of these adverse events.
- Suppression of the hypothalamus-pituitary axis - shunting of growth in children may occur

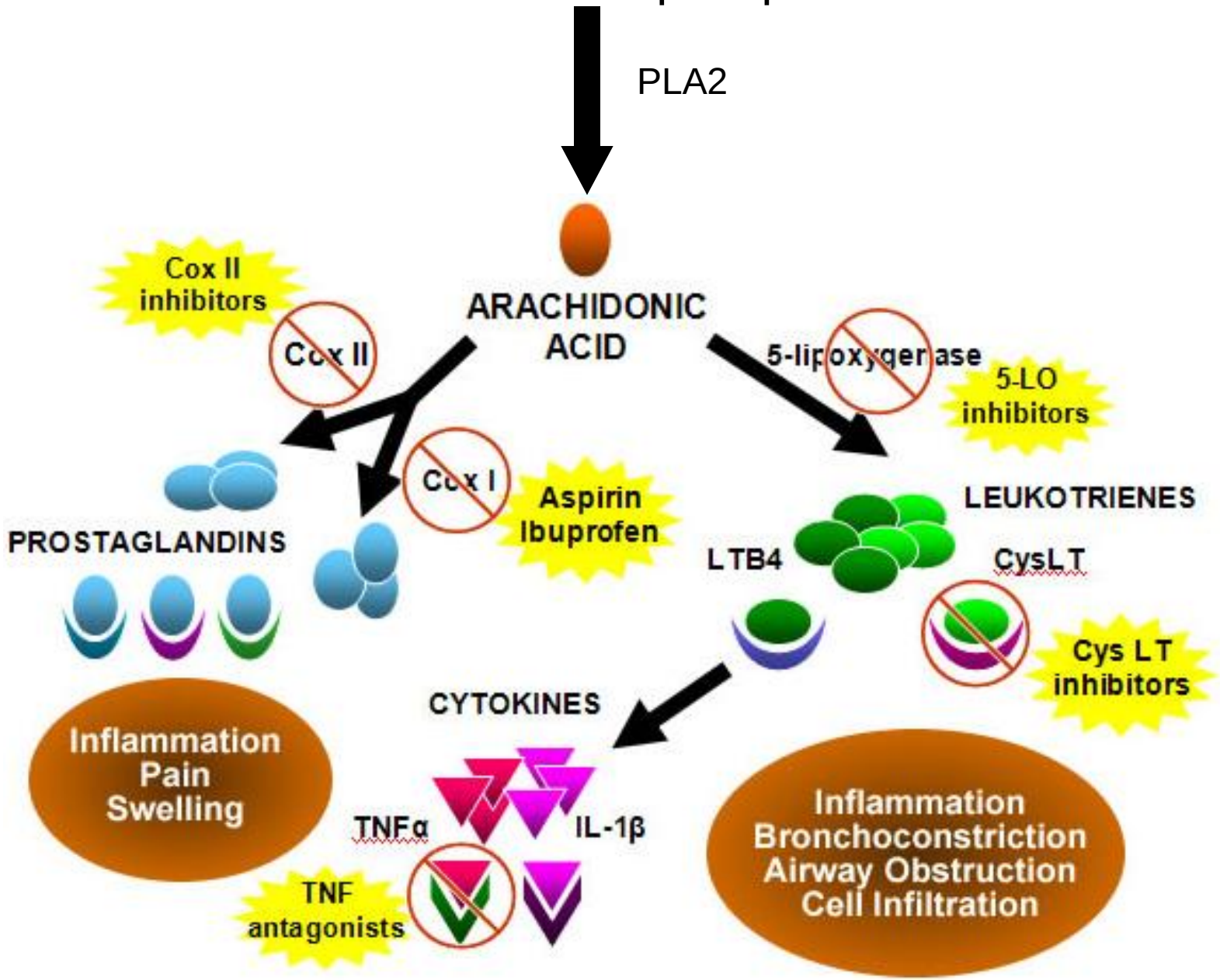
Alternative Drugs Used to Treat Asthma

These drugs are useful for treatment of:

- Moderate to severe allergic asthma
- Patients who are poorly controlled by conventional therapy or
- experience adverse effects secondary to high-dose or prolonged corticosteroid treatment.

These drugs should be used in conjunction with ICS therapy, **not** as sole therapies

Membrane Phospholipids



A. Leukotriene antagonists

- Leukotriene LTB4
- Cysteinyl leukotrienes: LTC4, LTD4, and LTE4

- They are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade.

- 5-Lipoxygenase is found in cells of myeloid origin, such as mast cells, basophils, eosinophils, and neutrophils.

Function of leukotrienes:

- **LTB4** is a potent chemoattractant for neutrophils and eosinophils

- **The cysteinyl leukotrienes:**
  - ✓ constrict bronchiolar smooth muscle
  - ✓ increase endothelial permeability
  - ✓ and promote mucous secretion.

Leukotriene modifiers

1. **Zileuton**

   - It is a selective and specific inhibitor of 5-lipoxygenase
   - It prevents the formation of both LTB4 and the cysteinyl leukotrienes.

2. **Zafirlukast and montelukast**

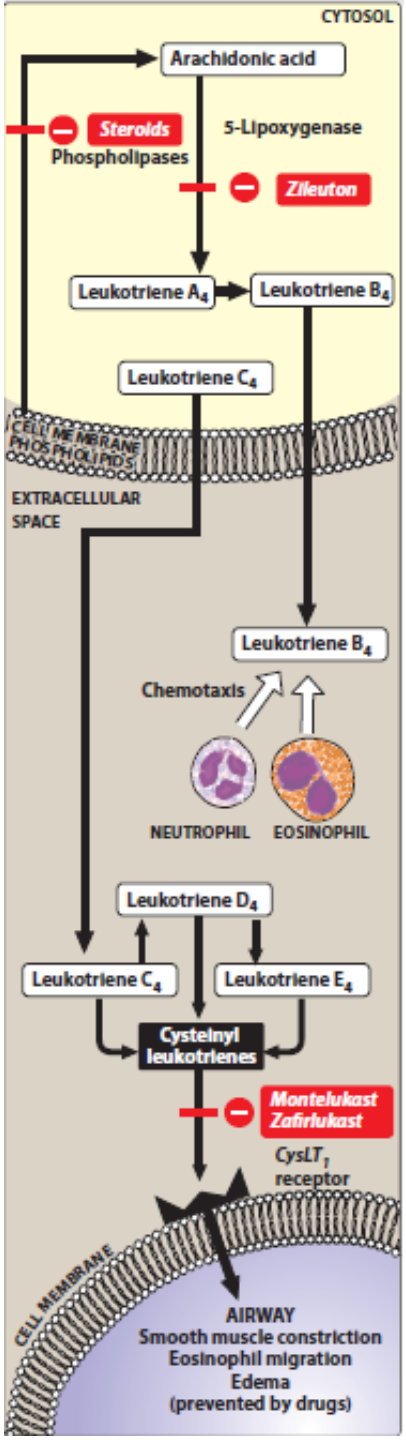
   - They are selective, reversible inhibitors of the cysteinyl leukotriene-1 receptor, thereby blocking the effects of cysteinyl leukotrienes.

- **Montelukast** has two primary advantages:

  1. dosing recommendations for children 1 year of age and older
  2. being available in chewable tablets and granule formulations.

- All three drugs are approved for the prophylaxis of asthma

- Not effective in situations where immediate bronchodilation is required.



Sites of action of leukotriene modifying drugs. CysLT1 = cysteinyl leukotriene-1.

Adverse effects:

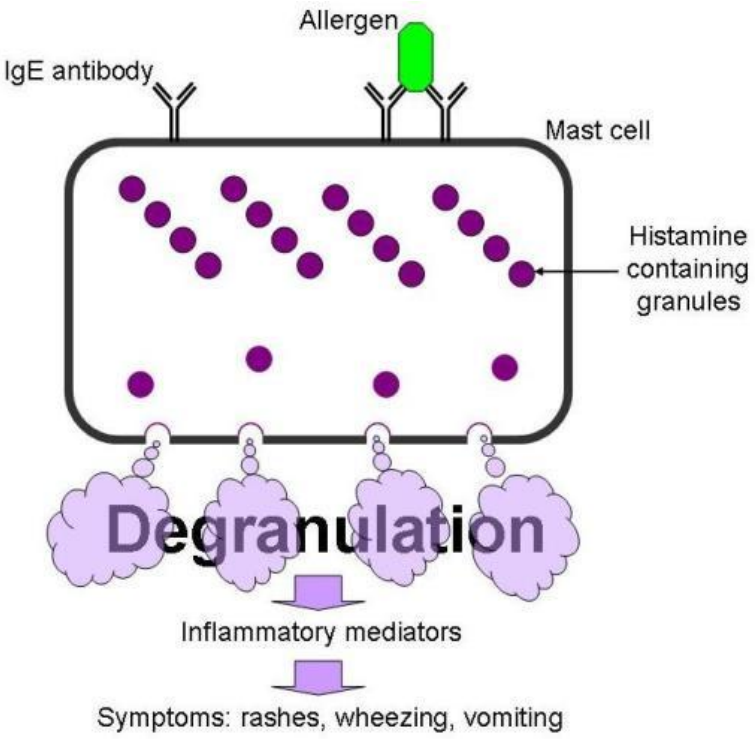
- Elevations in serum hepatic enzymes have occurred with all three agents, requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal.
- Eosinophilic vasculitis: rare
- Headache and dyspepsia.
- Both Zafirlukast and Zileuton are inhibitors of cytochrome P450.
- Both drugs can increase serum levels of warfarin.

B. Cromolyn and Nedocromil: ‘mast cell stabilizer’

Mechanism of action:

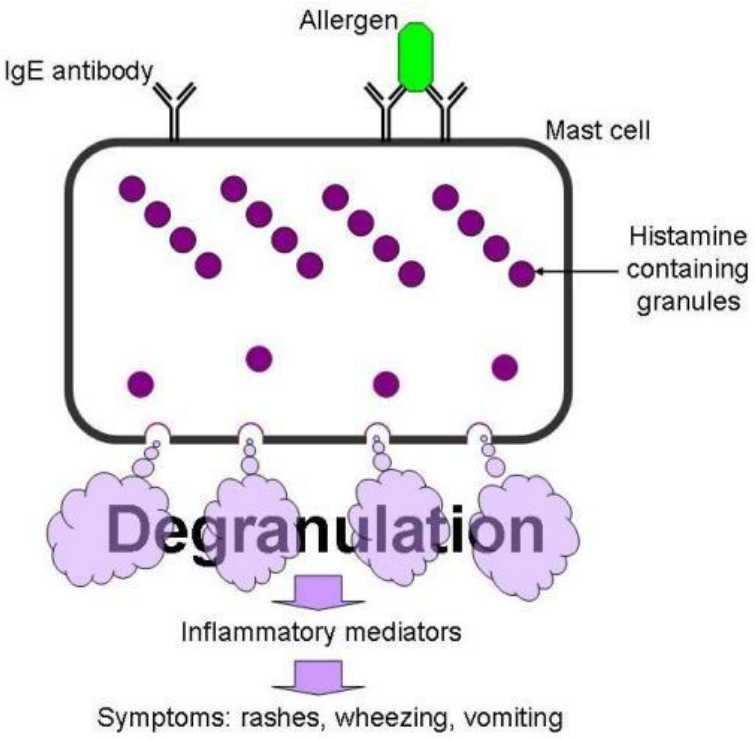
1. Prevents mast cell degranulation; prevent the release of inflammatory mediators including histamine.

2. Also probably suppress the response of exposed irritant nerves; effective for the treatment of ‘asthmatic cough’.



B. Cromolyn and Nedocromil: ‘mast cell stabilizer’

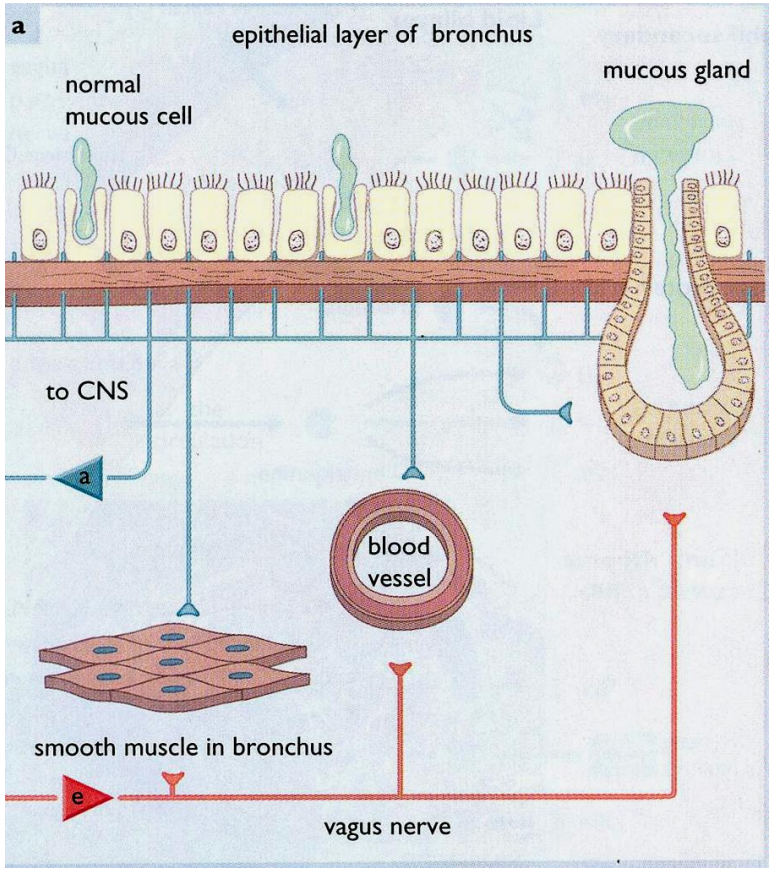
- Prophylactic anti-inflammatory agent
- Alternative therapy for mild persistent asthma.
- It is not useful in managing an acute asthma attack, because it is not a bronchodilator.



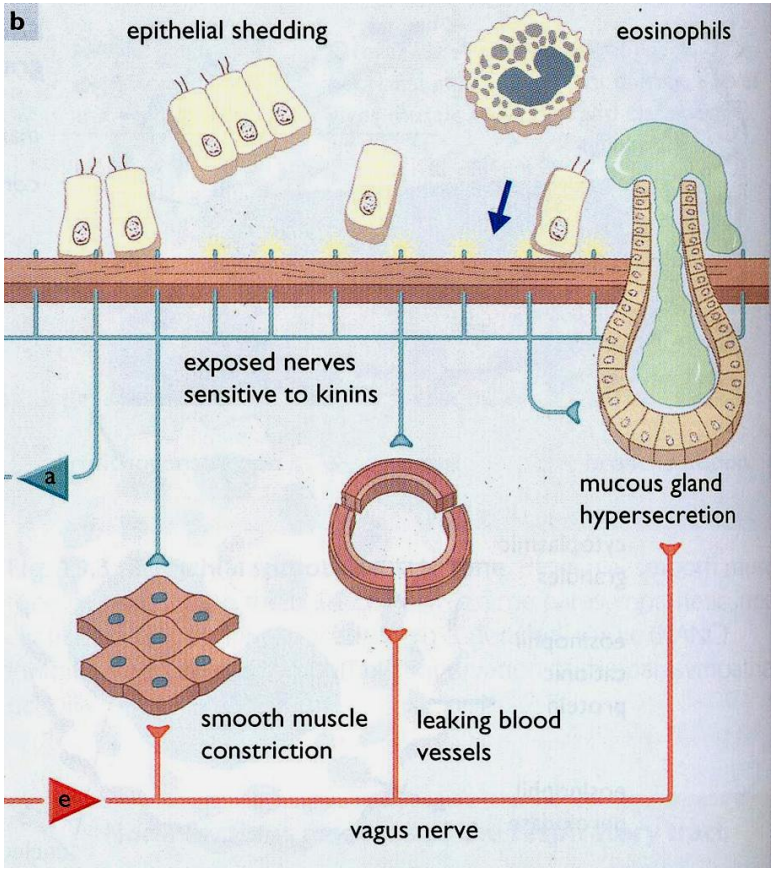
Side effects of Cromolyn

- Mild bitter taste
- irritation of the pharynx and larynx.

Cholinergic antagonists



Normal lung



Asthmatic lung

Cholinergic antagonists

- Less effective than β2-adrenergic agonists.

- They block the vagally mediated:
  - contraction of airway smooth muscle
  - mucus secretion.

- Inhaled ipratropium:
  - is useful in patients who are unable to tolerate adrenergic agonists.
  - slow in onset
  - nearly free of side effects.

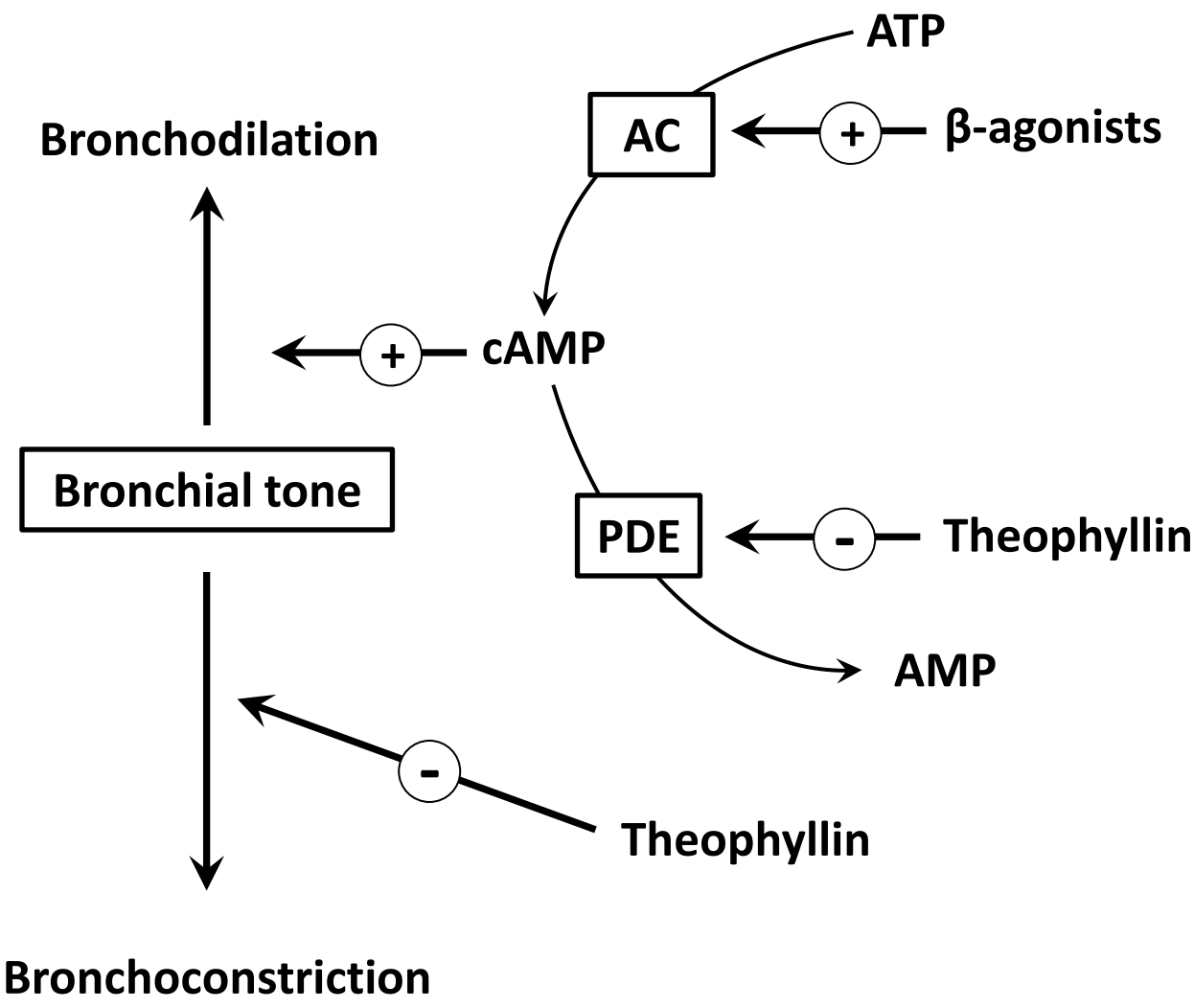
Methylxanthines

- Thyophyllin, Aminophyllin

- **Mechanism of Action**

  a. Phosphodiesterase inhibitor, therefore, increased cAMP -----relaxation
  b. blocks the action of adenosine

Mechanism of Action of Methylxanthins



Theophylline

- **Administration**: usually given orally, IV, rectally
- Kinetics – short biological half-life
  'slow-release' preparations

- **Side effects:**
  - It has narrow therapeutic window
  - Subject to numerous drug interactions via alteration of hepatic enzymes
  - Serum concentration monitoring should be performed when theophylline is used chronically
  - Fatal cardiac arrhythmias
  - Convulsions

Drug interactions of Thyophyllin

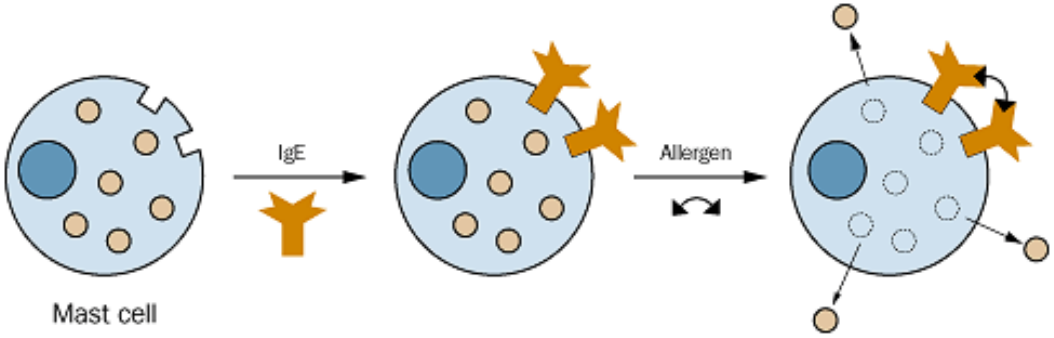
The serum theophylline concentration can be:

- **Decreased by:**
  - Barbiturates
  - Benzodiazepines

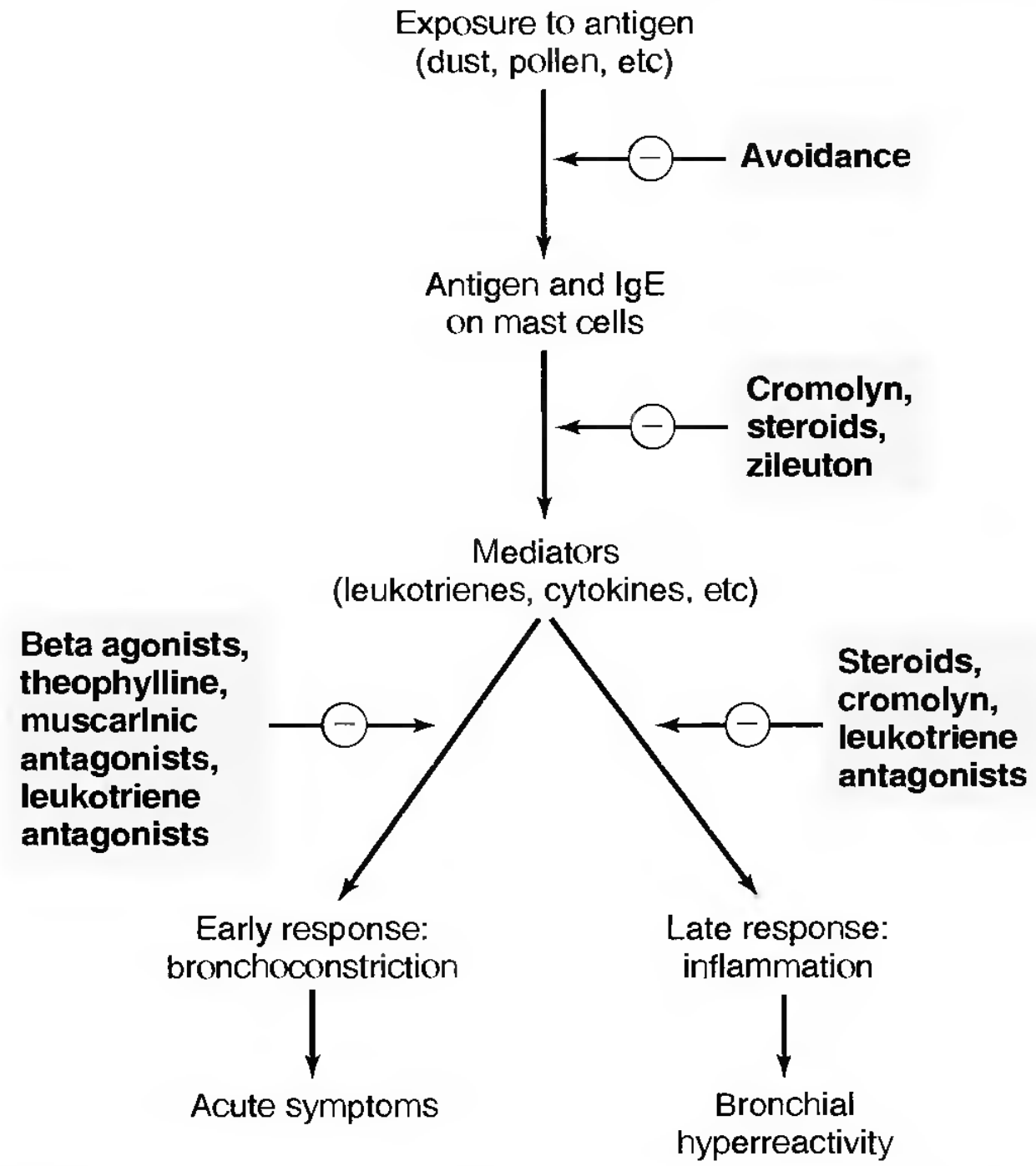
- **Increased by**
  - Erythromycin (for M. peumoniae)
  - Ciprofloxacin (for Gram –ve bacteria)
  - Allopurinol
  - Cimetidine

Omalizumab

- Recombinant DNA–derived monoclonal antibody
- Selectively binds to human immunoglobulin E (IgE).
- This leads to decreased binding of IgE to the high-affinity IgE receptor on the surface of mast cells and basophils.



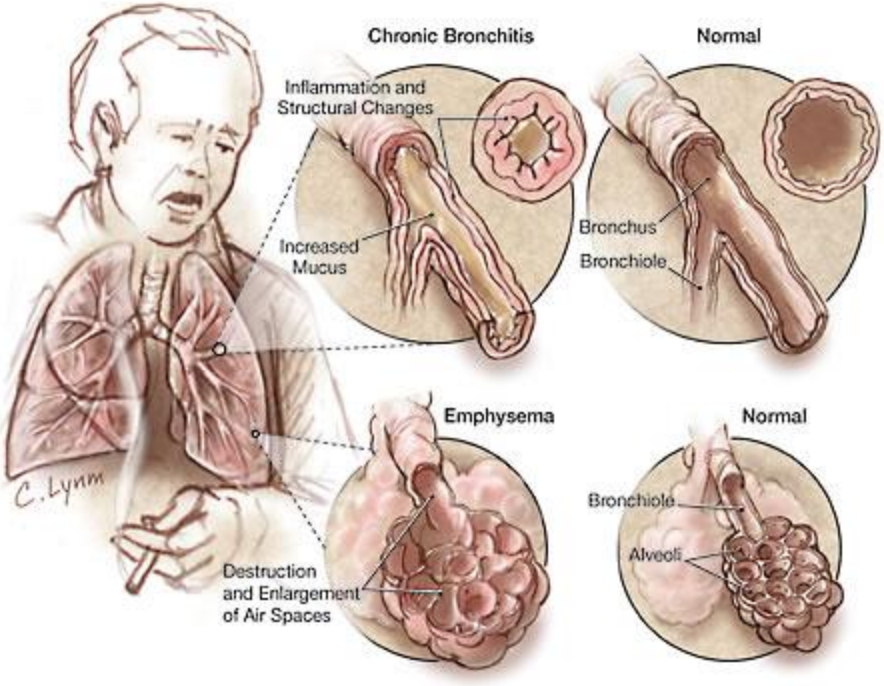
- **Use:** moderate to severe allergic asthma in patients who are poorly controlled with conventional therapy.


Exposure to antigen
(dust, pollen, etc)
Avoidance
Antigen and IgE
on mast cells
Cromolyn,
steroids,
zileuton
Mediators
(leukotrienes, cytokines, etc)
Beta agonists,
theophylline,
muscarinic
antagonists,
leukotriene
antagonists
Steroids,
cromolyn,
leukotriene
antagonists
Early response:
bronchoconstriction
Late response:
inflammation
Acute symptoms
Bronchial
hyperreactivity

Drugs Used to Treat Chronic Obstructive Pulmonary Disease

- Chronic obstructive pulmonary disease is a chronic, irreversible obstruction of airflow.

- Smoking is the greatest risk factor for COPD and is directly linked to the progressive decline of lung function as demonstrated by forced expiratory volume (FEV).



Treatment of COPD:

- **Inhaled bronchodilators:**
  - anticholinergic agents (ipratropium and tiotropium)
  - β2-adrenergic agonists

- **Pharmacological effects:**
  1. increase airflow
  2. alleviate symptoms
  3. decrease exacerbation of disease

- Combinations of an anticholinergic plus a β2 agonist may be helpful in patients for whom a single inhaled bronchodilator has failed to provide an adequate response.

- albuterol + ipratropium ⇨ greater bronchodilation than with either drug alone.

- Longer-acting drugs, such as Salmeterol and Tiotropium, have the advantage of less frequent dosing.

Guidelines for the pharmacologic therapy of stable COPD

PATIENT GROUP	RECOMMENDED FIRST CHOICE	ALTERNATIVE CHOICE
A Low risk Less symptoms	Short-acting anticholinergic when necessary or Short-acting β_2 agonist when necessary	Long-acting anticholinergic or Long-acting β_2 agonist or Short-acting β_2 agonist and short-acting anticholinergic
B Low risk More symptoms	Long-acting anticholinergic or Long-acting β_2 agonist	Long-acting anticholinergic and long-acting β_2 agonist
C High risk Less symptoms	Inhaled corticosteroid + long-acting β_2 agonist or Long-acting anticholinergic	Long-acting anticholinergic and long-acting β_2 agonist or Long-acting anticholinergic and PDE-4 inhibitor or Long-acting β_2 agonist and PDE-4 inhibitor
D High risk More symptoms	ICS + long-acting β_2 agonist and/or Long-acting anticholinergic	ICS + long-acting β_2 agonist and long-acting anticholinergic or ICS + long-acting β_2 agonist and PDE-4 inhibitor or Long-acting anticholinergic and long-acting β_2 agonist or Long-acting anticholinergic and PDE-4 inhibitor

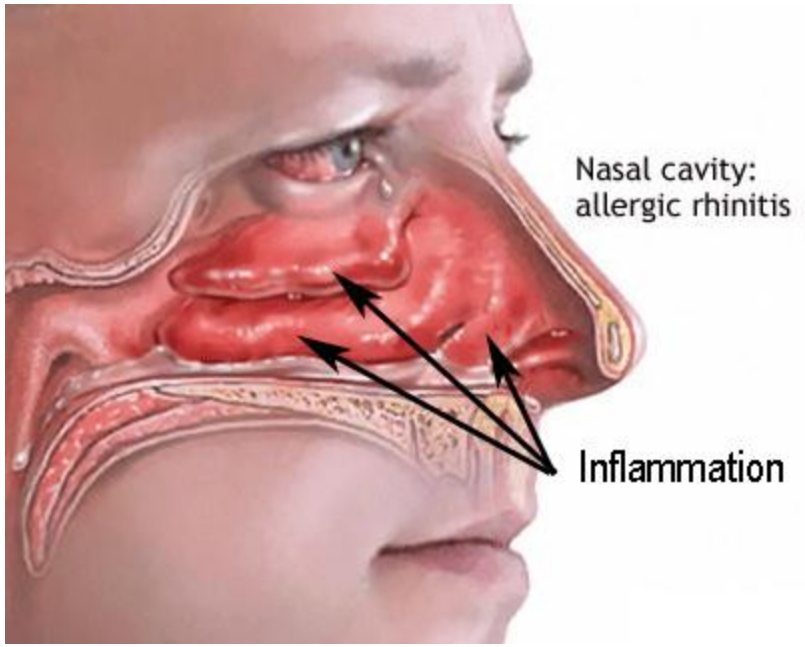
COPD = chronic obstructive pulmonary disease, ICS = inhaled corticosteroid, PDE-4 = phosphodiesterase-4
Note: Risk denotes risk of COPD exacerbations.

Drugs Used to Treat Allergic Rhinitis

Allergic Rhinitis

- Rhinitis is an inflammation of the mucous membranes of the nose and is characterized by:
  - Sneezing
  - Itchy nose/eyes
  - Watery rhinorrhea
  - Nasal congestion

- An attack may be precipitated by inhalation of an allergen (such as dust, pollen, or animal dander).



Allergic Rhinitis

- The foreign material interacts with mast cells coated with IgE generated in response to a previous allergen exposure .

- The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors, that promote:
  - bronchiolar spasm
  - mucosal thickening from edema and cellular infiltration.

Drugs Used to Treat Allergic Rhinitis

- Antihistamines and/or intranasal corticosteroids are preferred therapies for allergic rhinitis

- Systemic effects associated with these oral preparations (sedation, insomnia, and, rarely, cardiac arrhythmias) have prompted interest in topical intranasal delivery of drugs.

Intranasal corticosteroids

- Beclomethasone, Budesonide, Fluticasone, Mometasone, and Triamcinolone
- Most effective medications for treatment of allergic rhinitis.
- They improve sneezing, itching, rhinorrhea, and nasal congestion.
- Systemic absorption is minimal
- Side effects of intranasal corticosteroid treatment are localized.

Intranasal corticosteroids

- **Side effects include:** nasal irritation, nosebleed, sore throat, and, rarely, candidiasis.

- To avoid systemic absorption, patients should be instructed **not to** inhale deeply while administering these drugs because the target tissue is the nose, not the lungs or the throat.

- For patients with chronic rhinitis, improvement may not be seen until 1 to 2 weeks after starting therapy

Antihistamines

Antihistamines (H1-receptor blockers)

- Useful for the management of histamine-mediated symptoms (sneezing, watery rhinorrhea, itchy eyes/nose).
- They are more effective for prevention of symptoms
- Ophthalmic and nasal antihistamine delivery devices are available for more targeted tissue delivery.
- **First-generation antihistamines**, such as diphenhydramine and chlorpheniramine, are usually not preferred
- **Adverse effects of first-gen**.: sedation, performance impairment, anticholinergic effects (dry eyes/mouth, difficulty urinating and/or constipation.

Antihistamines (H1-receptor blockers)

- **The second-generation antihistamines:** Fexofenadine, Loratadine, Cetirizine

- Better tolerated.

- Combinations of antihistamines with decongestants are effective when congestion is a feature of rhinitis.

α-Adrenergic agonists

- Short-acting: Phenylephrine
- Longer-acting: Oxymetazoline

- Mechanism of action: constrict dilated arterioles in the nasal mucosa and reduce airway resistance.

- When administered as an aerosol, these drugs have a rapid onset of action and show few systemic effects.

α-Adrenergic agonists

- Should be used no longer than 3 days due to the risk of rebound nasal congestion (rhinitis medicamentosa).
- For this reason, the α-adrenergic agents have no place in the long-term treatment of allergic rhinitis.
- Oral α-adrenergic agonist formulations results in a longer duration of action but also increased systemic effects.
- Regular use of **oral** α-adrenergic agonists (phenylephrine and pseudoephedrine) alone or in combination with antihistamines is not recommended

Intranasal Cromolyn

- Useful in allergic rhinitis, particularly when administered before contact with an allergen.

- Dosing should begin at least 1 to 2 weeks prior to allergen exposure.

Drugs Used to Treat Cough (Antitussives)

1. **Codeine:**

   - Decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli
   - Decreases mucosal secretion

- These effects occur at doses lower than those required for analgesia.

- **Sides effects:**
  - Constipation
  - Dysphoria: restlessness
  - Fatigue
  - Addictive potential

2. Dextromethorphan:

- Suppresses the response of the central cough center.
- It has no analgesic effects
- has a low addictive profile
- may cause dysphoria at high doses, which may explain its status as a potential drug of abuse.

- Cough suppression: Dextromethorphan **=** Codeine