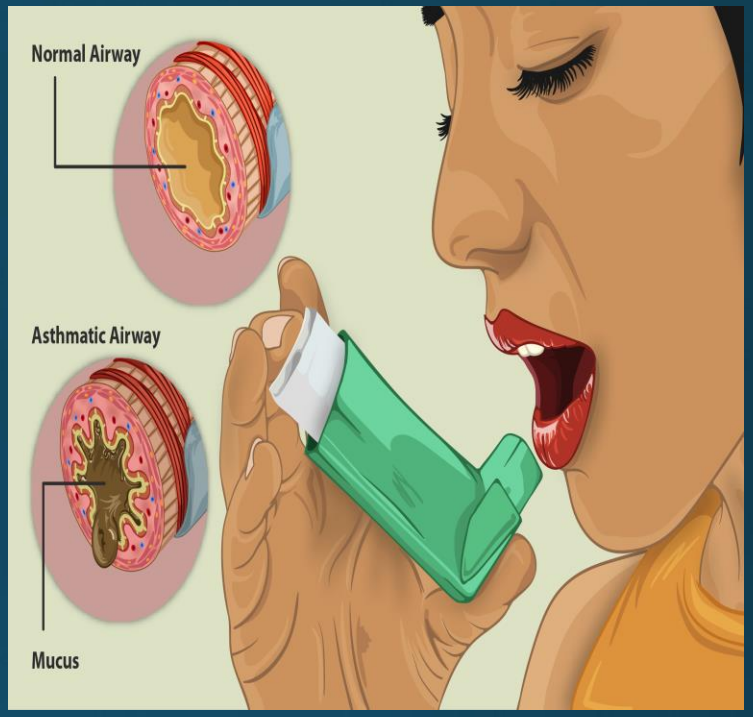
Anti asthmatic drugs



Presented by

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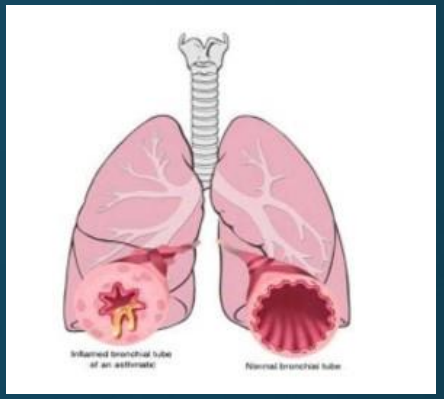
MBBS ,M.Phil, PhD(1)
Assistant professor
Pharmacology deptt ANMC

Learning objectives

At the end of this lecture, students will be able to know about:

- Definition, epidemiology ,Pathophysiology and types of asthma
- Diagnosis and management of asthma
- Classification of antiasthmatic drugs
- Mechanism of action, adverse effects, and clinical uses of antiasthmatic drugs
- Step wise approach for different types of asthma
- Treatment of status asthmaticus
- Newer drugs

Bronchial Asthma



Bronchial Asthma is a chronic disease with an underlying lymphocytic, eosinophilic inflammation of the bronchial mucosa in airways; not fully reversible

. Incidence of bronchial asthma : 5-10%.

ASTHMA

About
300 million
in the world

CAUSES

- PET DANGER
- AIR POLLUTANTS
- SOME FOODS AND BEVERAGES
- RESPIRATORY INFECTIONS
- CERTAIN MEDICATIONS
- SMOKING
- CHEMICALS AND PARFUMES
- STRESS
- DUST

SYMPTOMS

CAUSES

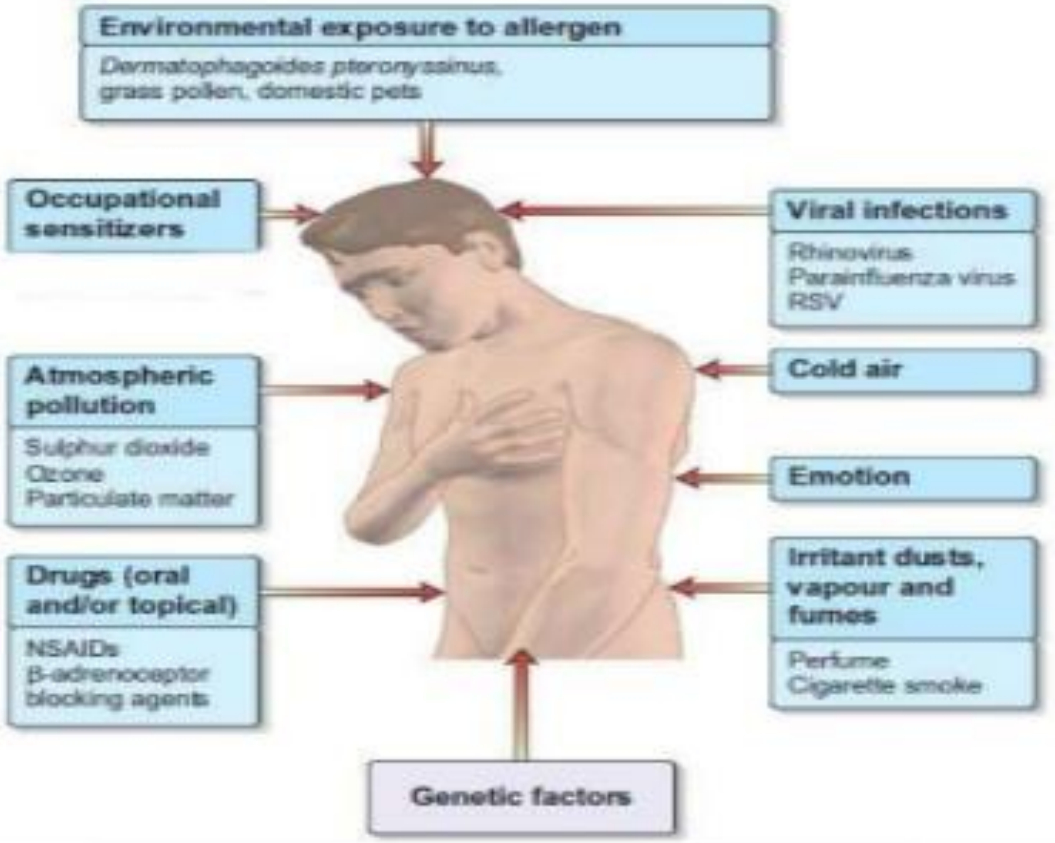
Asthma may be triggered because of :

1)Environmental Factors:

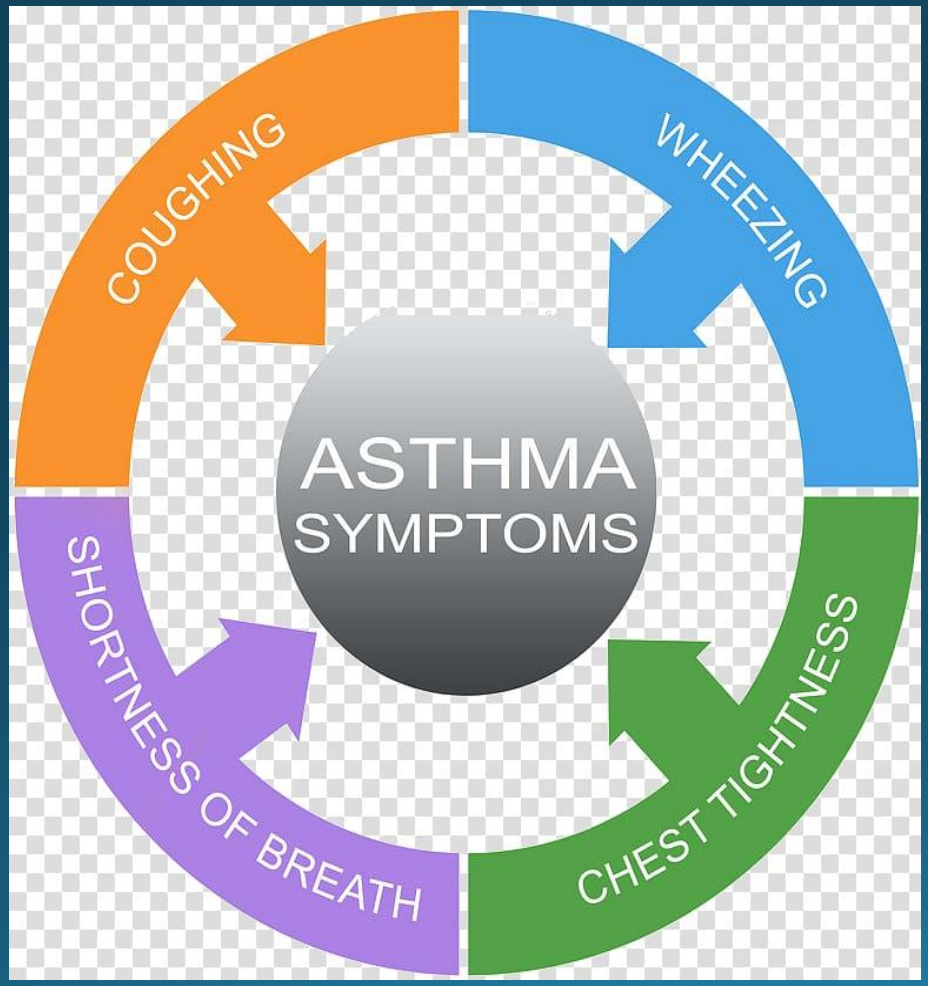
- Air pollutants
- Smoking
- Dust
- Pets
- Chemicals

2)Genetic Factors:

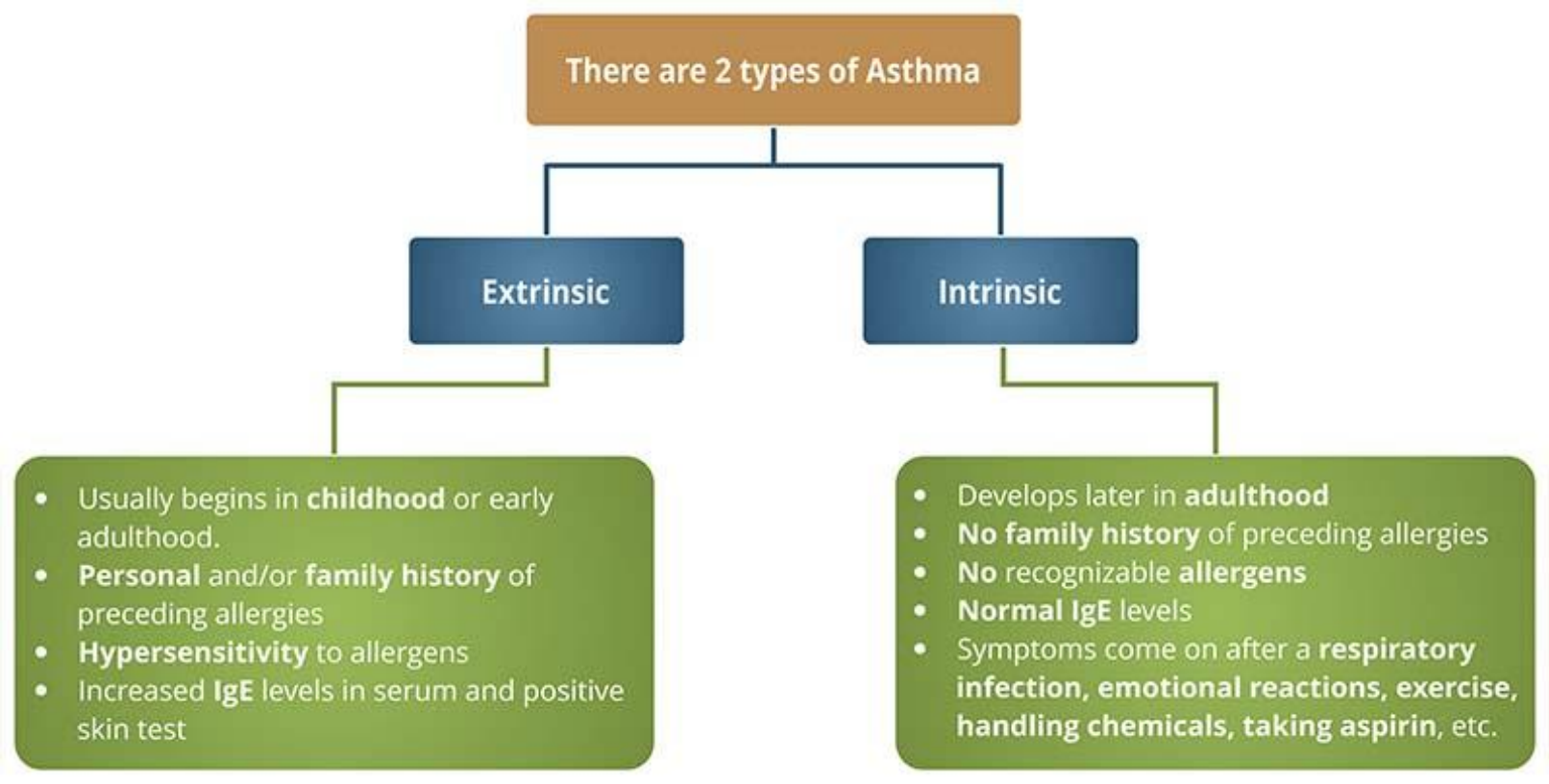
- Family history
- Certain genes



Signs and symptoms



Types of bronchial asthma



Bronchial asthma Classifications

Asthma may be categorized into types

1- Atopic type (**allergic sensitization**, **Extrinsic**).

2 - Non-atopic type (**No allergic sensitization**).

3- Bronchoconstriction triggering agents - include

(a) **Seasonal** asthma (b) **Exercise-induced** asthma.
(c) **Drug-induced** asthma (e.g., **aspirin & NSAID**).
(d) **Occupational** asthma
(e) Eemotional asthma .
(f) **Asthmatic bronchitis** in smokers.

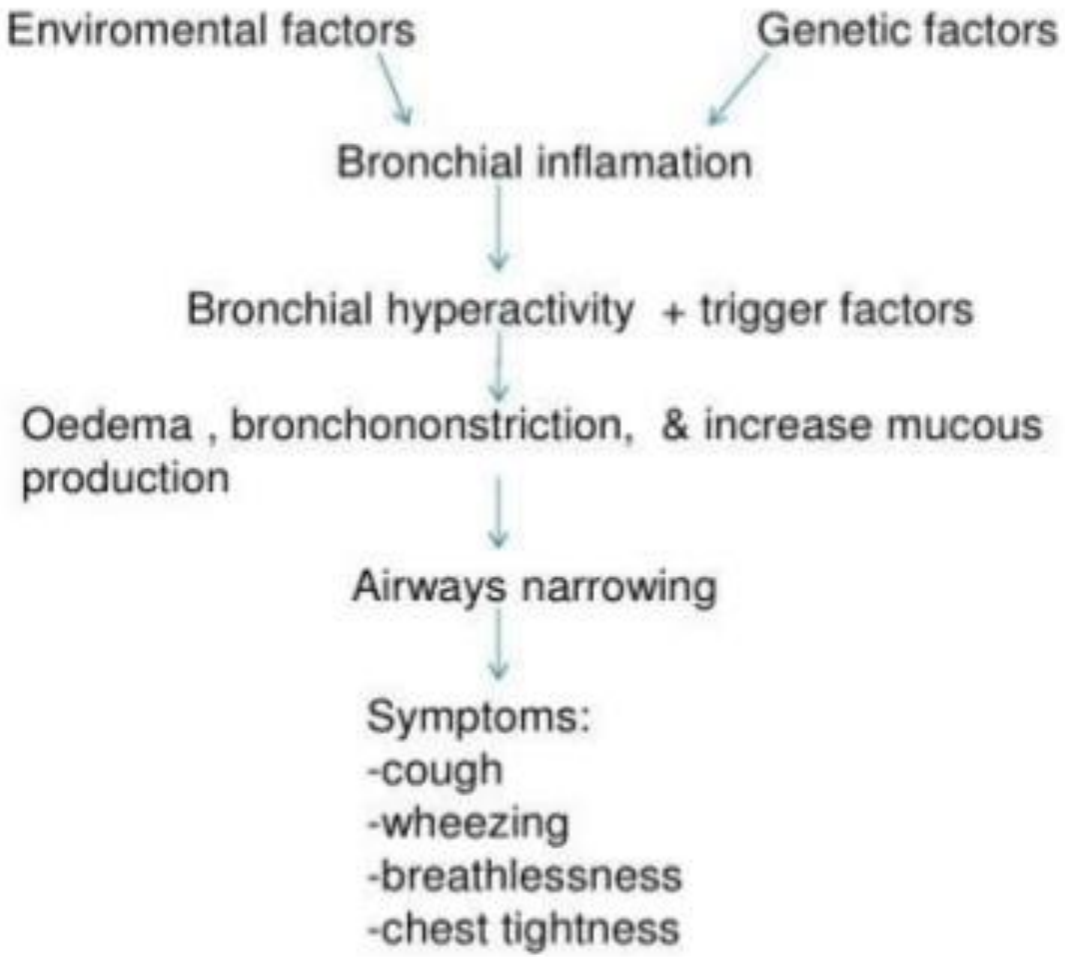
4-Recent studies added three subphenotypes of Asthma , based on **Airway inflammation pattern**

Pathophysiology of asthma

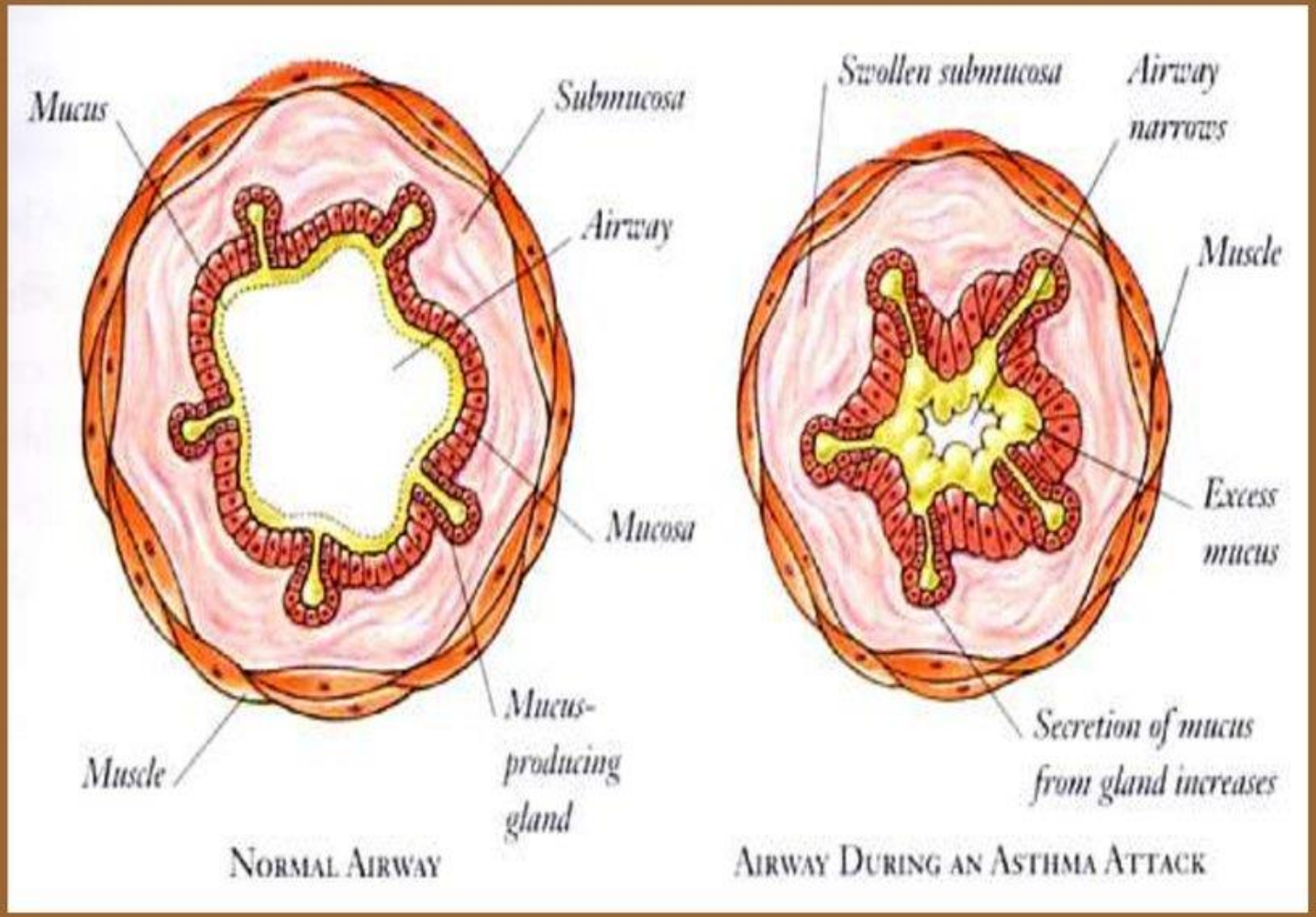
- Physiologically Asthma is characterized by wide spread reversible narrowing of the airways & a marked increase in bronchial responsiveness to inhaled stimuli.

- May be progressive, airway remodeling may occur.(thickening of the lamina reticularis beneath the airway epithelium & hyperplasia of the cells of all structural elements of the airway wall BV,SM & glands).

Pathogenesis of asthma

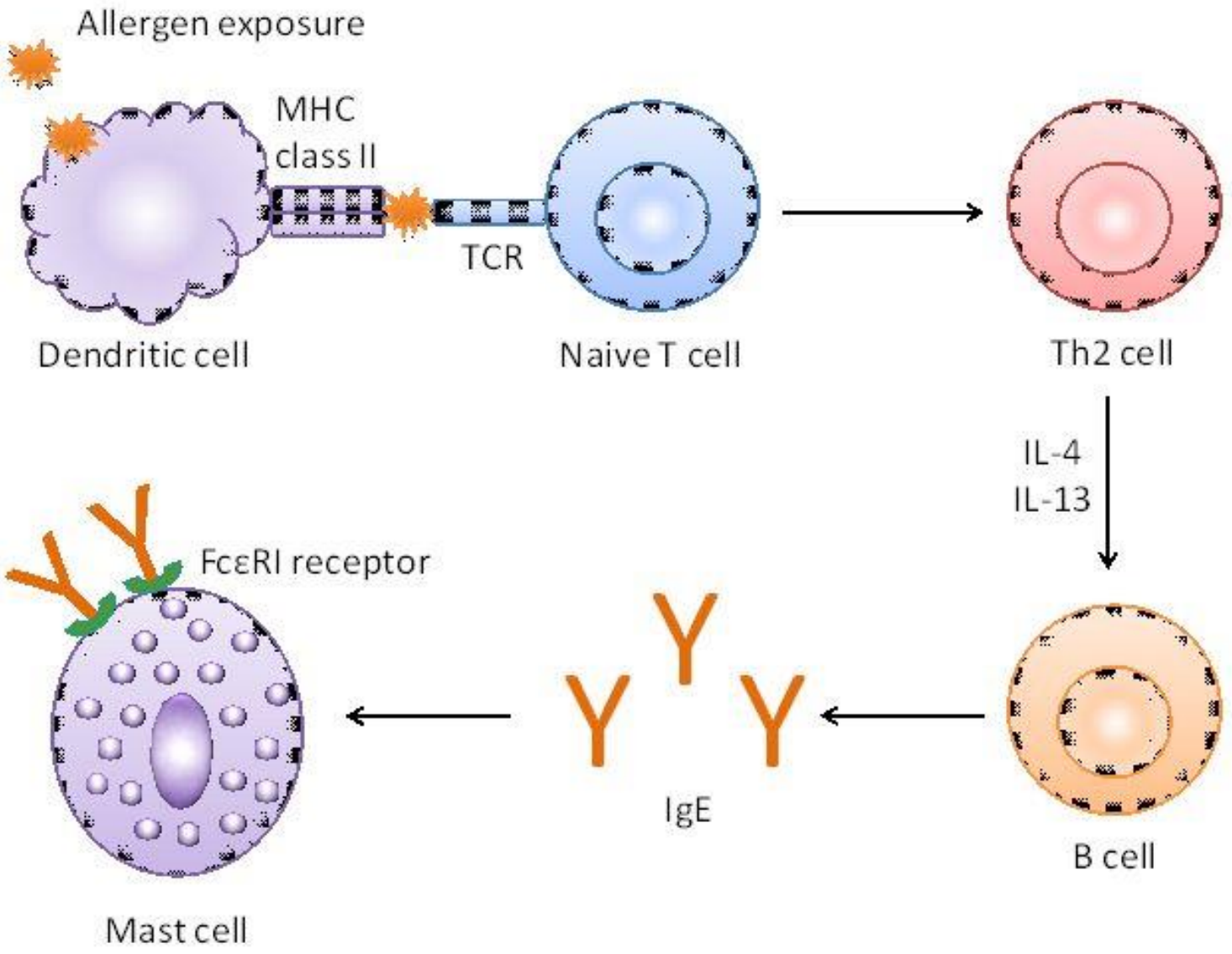


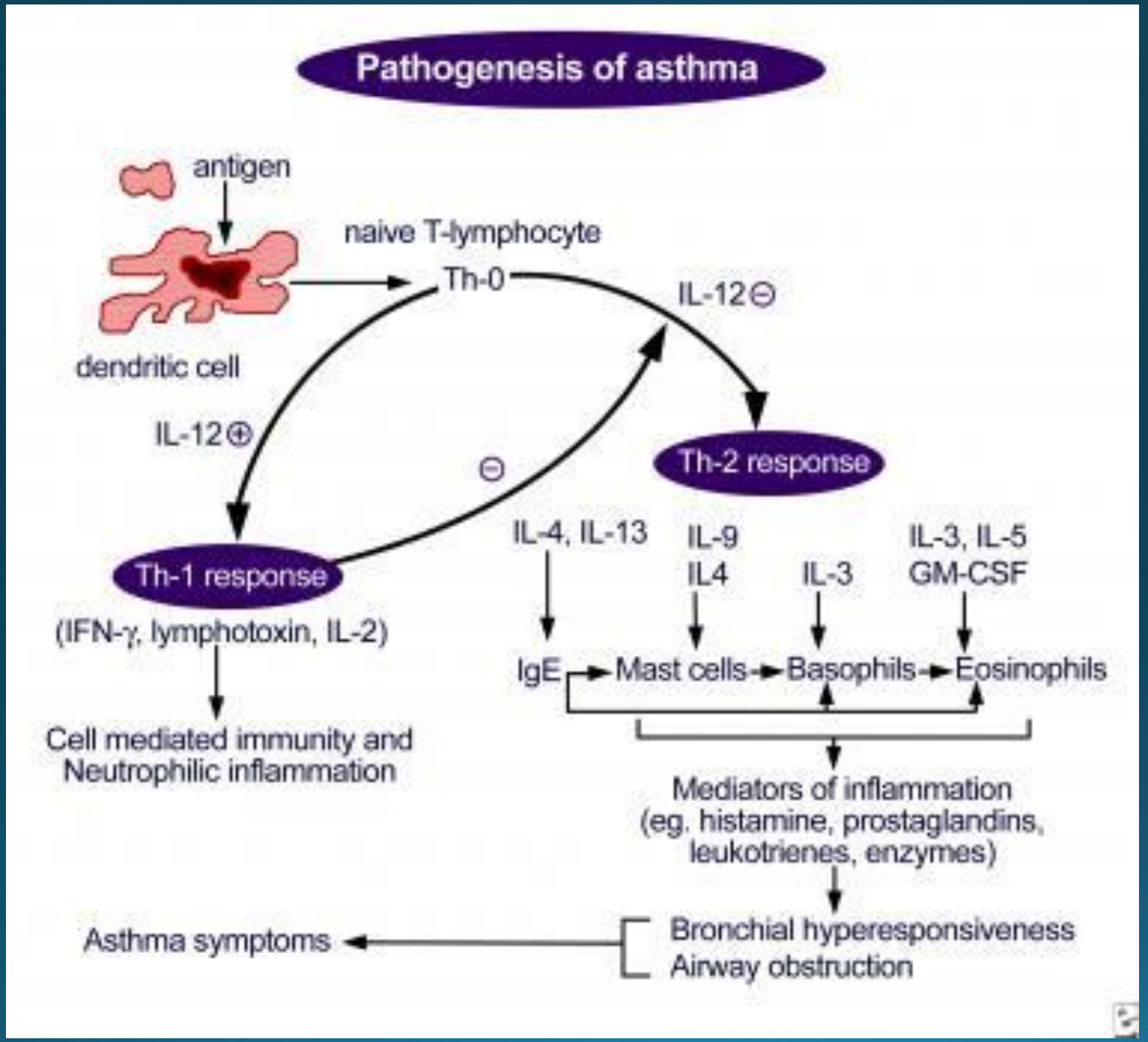
ASTHMA : PATHOLOGY



PATHOPHYSIOLOGY

- ***EARLY RESPONSE***
- contraction of air way. muscle
- ***LATE RESPONSE***
- mucosal thickening_ edema
- mucus hypersecretion
- inc.br. reactivity
- **remodeling** of mucosa –coll. hyper.


Allergen exposure
MHC
class II
TCR
Dendritic cell
Naive T cell
Th2 cell
IL-4
IL-13
FcεRI receptor
IgE
B cell
Mast cell


Pathogenesis of asthma
antigen
naive T-lymphocyte
Th-0
IL-12⊖
dendritic cell
IL-12⊕
⊖
Th-2 response
IL-4, IL-13
IL-9
IL4
IL-3
IL-3, IL-5
GM-CSF
Th-1 response
(IFN-γ, lymphotoxin, IL-2)
IgE
Mast cells
Basophils
Eosinophils
Cell mediated immunity and
Neutrophilic inflammation
Mediators of inflammation
(eg. histamine, prostaglandins,
leukotrienes, enzymes)
Asthma symptoms
Bronchial hyperesponsiveness
Airway obstruction

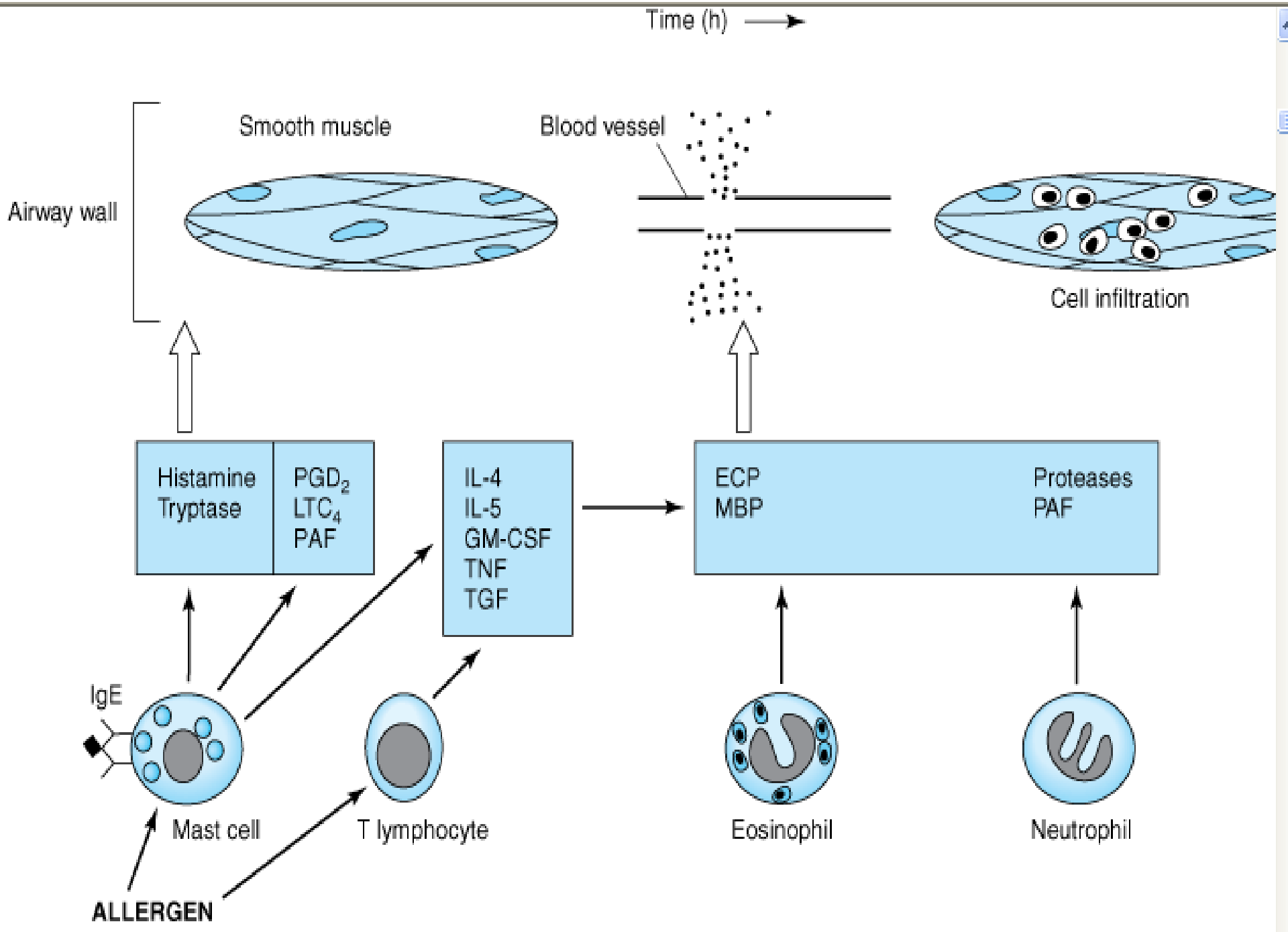
Immunopathogenesis of Asthma

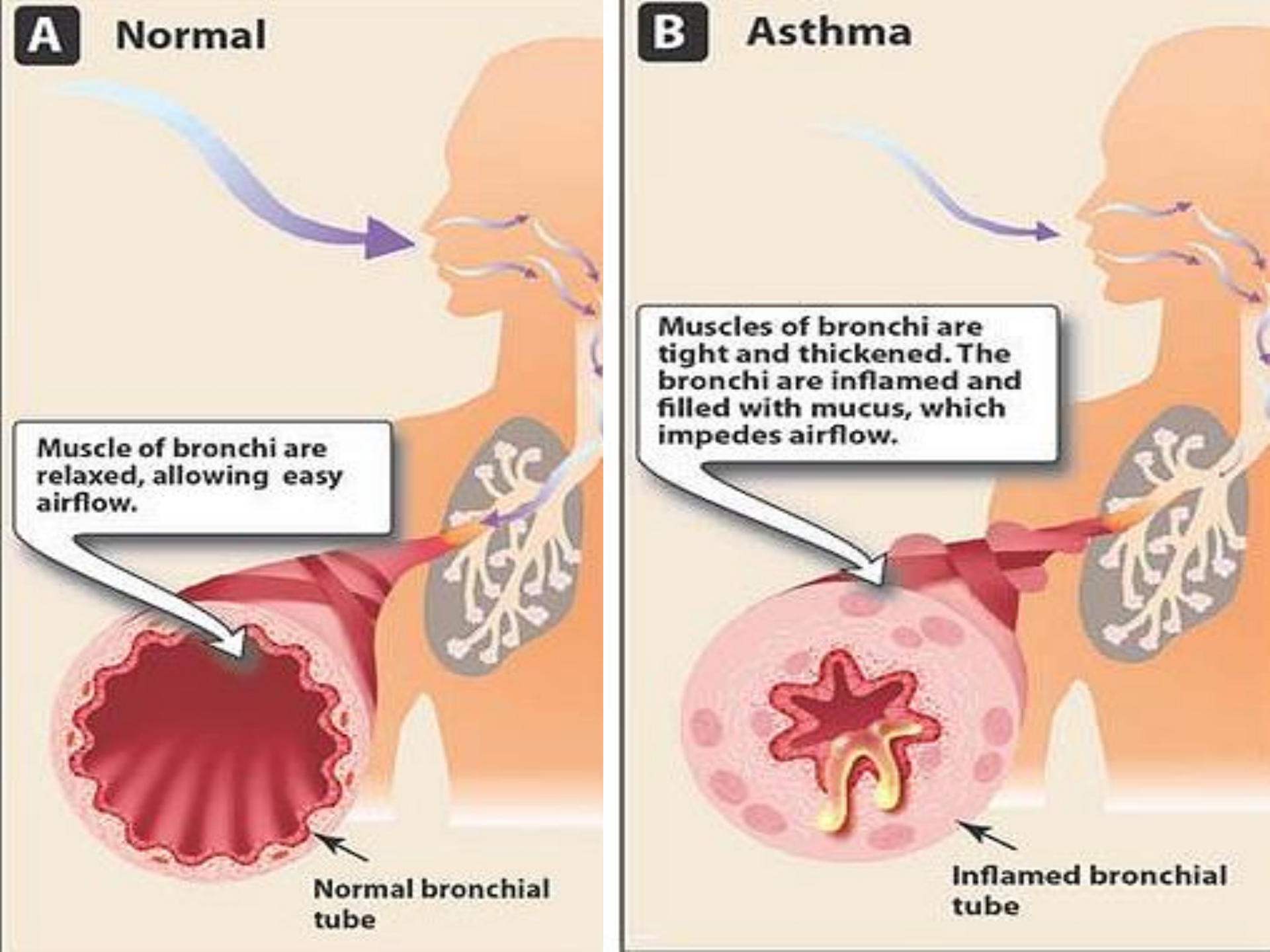
- Exposure to allergen causes synthesis of IgE which binds to mast cells in the airway mucosa.
- On re-exposure antigen –antibody reaction on mast cells surfaces triggers relase of mediators--- histamine,tryptase, PGD_4, LTC_4 & PAF.
- These agents provoke contraction of smooth muscles; producing immidiate bronchoconstriction; indicated by decline in FEV1.

Continued..

- Re-exposure to antigen also causes synthesis & release of many cytokines like LT 4 & 5, GM-CSF,TNF& tissue- GF from T-cells & mast cells.

- These cytokines activate eosinophils & neutrophils---- leading to production of further mediators ;which produce edema, mucus hypersecretion, SM contraction& increase in bronchial reactivity --late phase shown by decline in FEV1 2-8 hrs after exposure.


Time (h)
Smooth muscle
Blood vessel
Airway wall
Cell infiltration
Histamine
Tryptase
PGD2
LTC4
PAF
IL-4
IL-5
GM-CSF
TNF
TGF
ECP
MBP
Proteases
PAF
IgE
Mast cell
T lymphocyte
Eosinophil
Neutrophil
ALLERGEN


A Normal
Muscle of bronchi are relaxed, allowing easy airflow.
Normal bronchial tube
B Asthma
Muscles of bronchi are tight and thickened. The bronchi are inflamed and filled with mucus, which impedes airflow.
Inflamed bronchial tube

If untreated:

i. May be ↑ severity and ↑ incidence of exacerbations--- increased morbidity; increased hospitalizations; absence from school, offices, work place.

ii. Some patients can have sudden severe attack of Bronchial Asthma **(Status Asthmaticus)**, characterized by:

- ✓ Persistent dyspnea, poorly relieved by bronchodilators.
- ✓ Restlessness.
- ✓ Exhaustion
- ✓ High pulse rate.

ii. Death is rare

Diagnostic Testing

- Complete blood count
- Chest x ray ,,,, hyperinflation chest
- IgE level
- Sinus xray not routinely used
- Gold stander spirometry
- FEV1/FVC < 80%
- Bronchodilator ,,,, > 12%
- Exercise ,,,,,, < 15%
- Peak expiratory flow (PEF) ..... < 20 %
  - Inexpensive

Approaches to treatment of Bronchial Asthma

1.For an acute attack--- give bronchodilators.

2. Suppression of inflammation & bronchial reactivity.

For prevention:

3. Prevention of antigen –antibody reaction, avoidance of antigen, hypo sensitization—if allergen can be identified.

4. Antagonism of released mediators.

5. Neutralization of IgE.

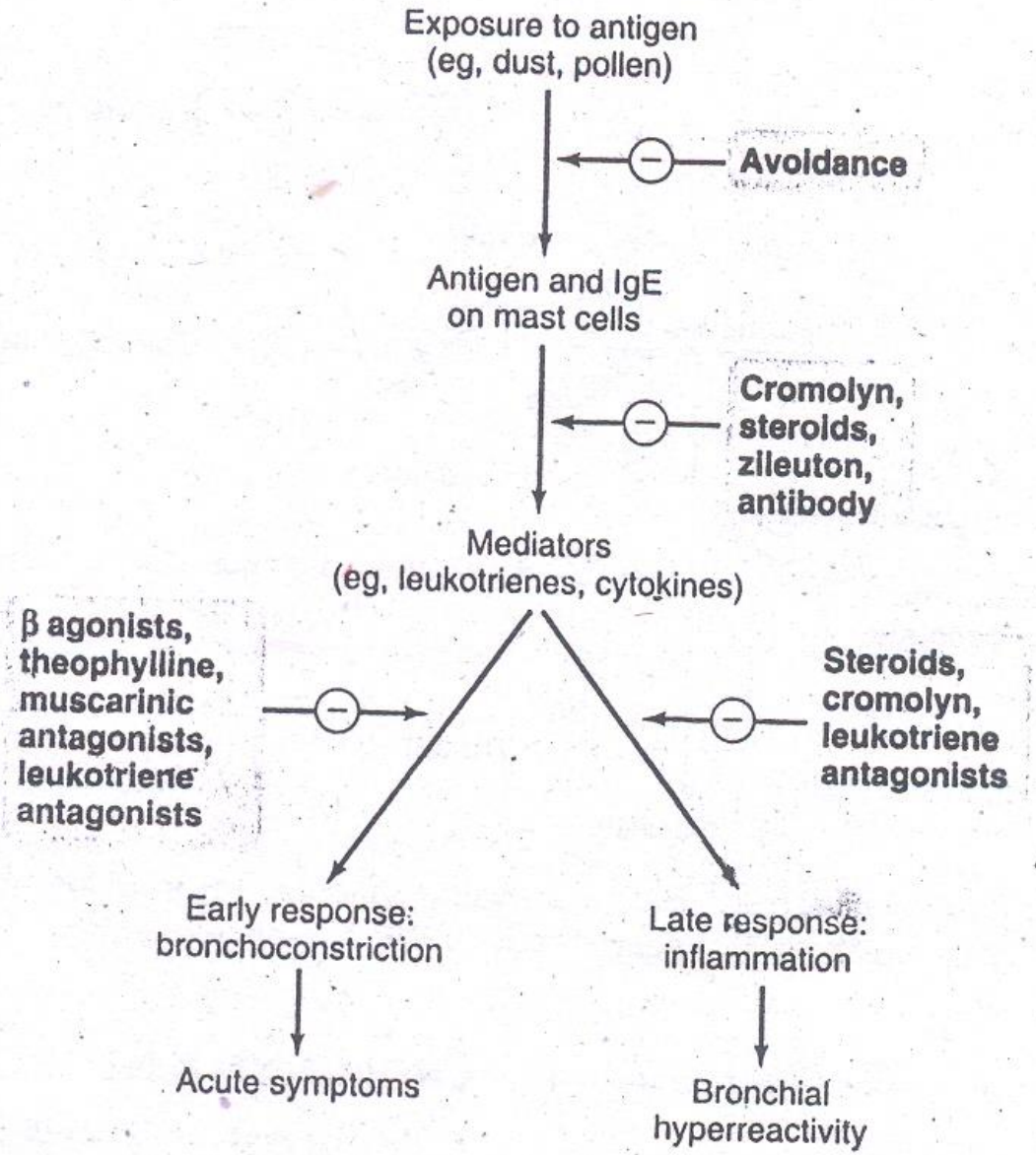


Figure 20–3. Summary of treatment strategies in asthma. (Modified and redrawn from Cockcroft DW: The bronchial late response in the pathogenesis of asthma and its modulation by therapy. *Allergy Asthma Immunol* 1985;55:857.)

DRUGS USED IN BRONCHIAL ASTHMA

- bronchodilators
- anti-inflamatory agents
- mast cell stablizer
- coticosteroids
- leukotriene antagonists
- anti IgE monoclonal antibodies

IN OUR LAST LECTURE WE HAVE DISCUSSED

- Asthma Definition
- epidemiology,causes
- types and pathophysiology

IN TODAYS LECTURE WE WILL DISCUSS:

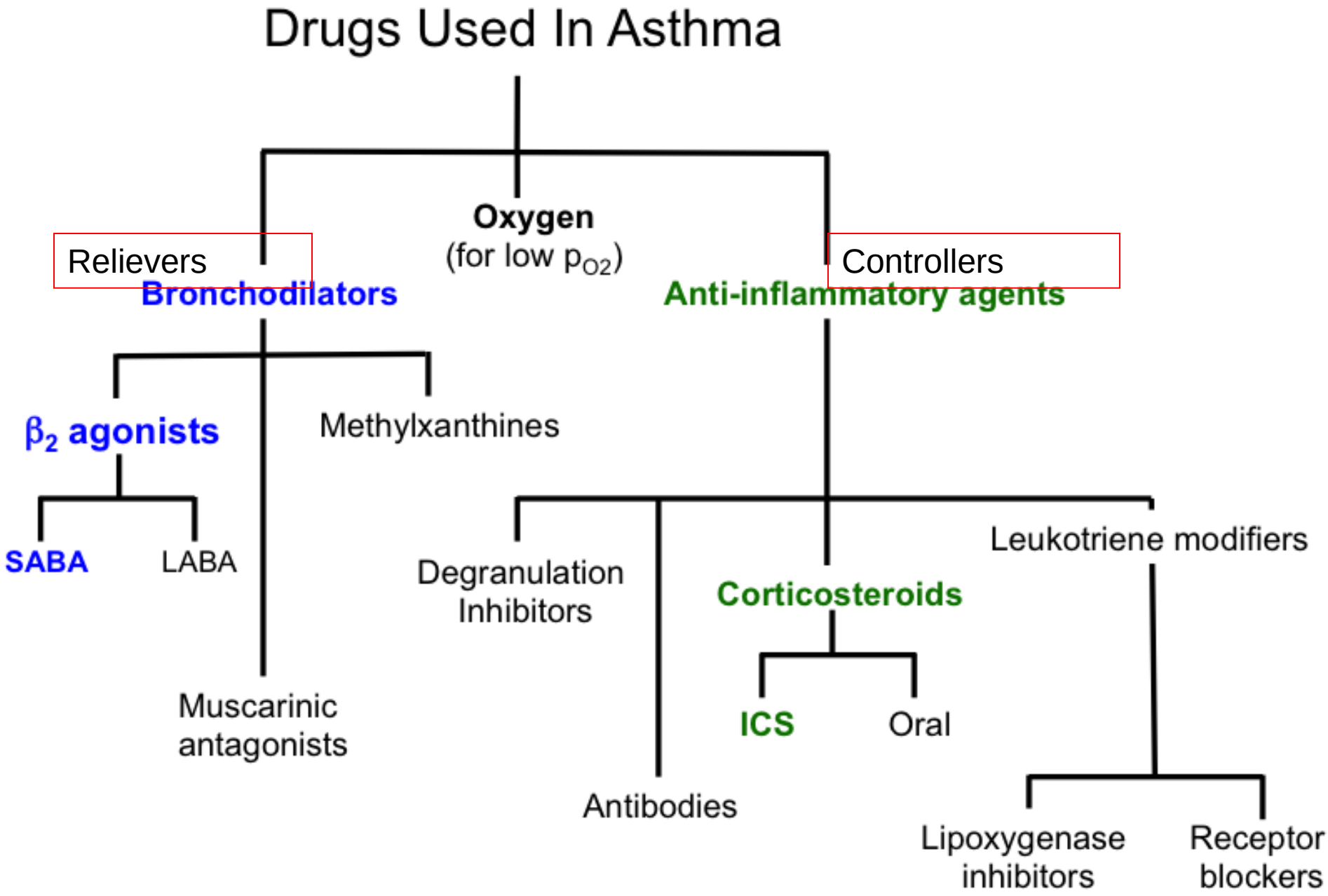
Classification of anti asthmatic drugs

- Bronchodilators, their types
- MOA, adverse effects and clinical uses of bronchodilators

CLASSIFICATION OF DRUGS USED IN BRONCHIAL ASTHMA

DRUGS USED IN BRONCHIAL ASTHMA

- bronchodilators
- anti-inflamatory agents
- mast cell stablizer
- coticosteroids
- leukotriene antagonists
- anti IgE monoclonal antibodies


Drugs Used In Asthma
Oxygen
(for low p_{O2})
Relievers
Controllers
Bronchodilators
Anti-inflammatory agents
β_2 agonists
Methylxanthines
SABA
LABA
Muscarinic antagonists
Degranulation Inhibitors
Corticosteroids
Leukotriene modifiers
ICS
Oral
Antibodies
Lipoxygenase inhibitors
Receptor blockers

BRONCHODILATORS

BRONCHODILATORS

Relievers

β AGONISTS

ISOPROTERENOL
TERBUTALINE
ALBUTEROL
METAPROTERENOL
PIRBUTEROL

SABA

SALMETEROL…LABA

FORMETEROL

MUSCARINIC ANTAGONISTS

IPRATROPIUM
TIOTROPIUM

METHYLXANTHINES

THEOPHYLLINE
THEOBROMINE
CAFFEINE
AMINOPHYLLINE

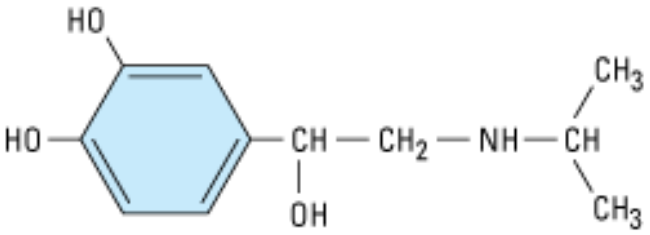
BETA AGONISTS

BRONCHODILATORS
RELIEVERS

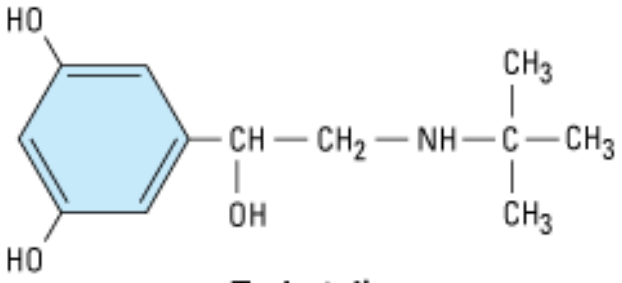
- **SELETIVE B2 AGONIST**
- albuteral
- terbutaline
- metaproterenol
- pirbuterol
- salmeterol
- formeterol

NON SELECTIVE SYMPATHOMIMETICS ***RELIEVERS***

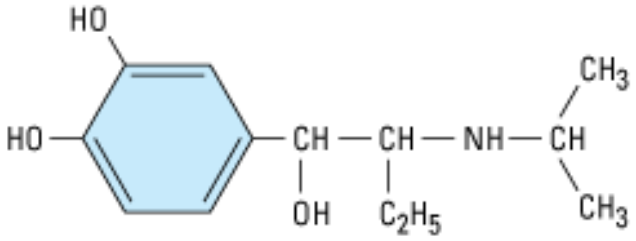
- ISOPROTERENOL (β1; β2)
- EPINEPHRINE(α , β)
- EPHEDRINE



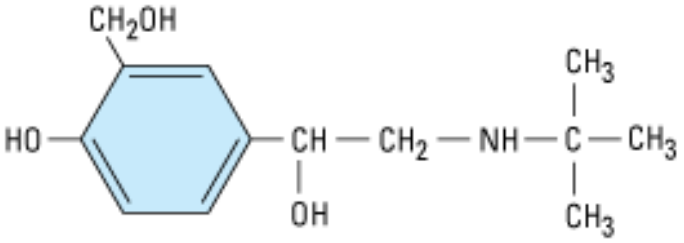
Isoproterenol



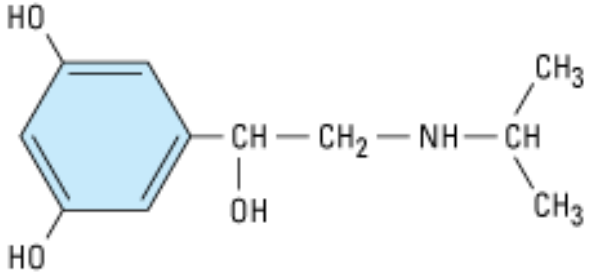
Terbutaline



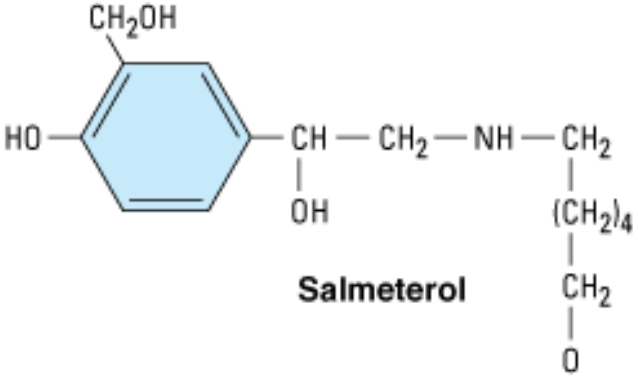
Isoetharine



Albuterol (salbutamol)



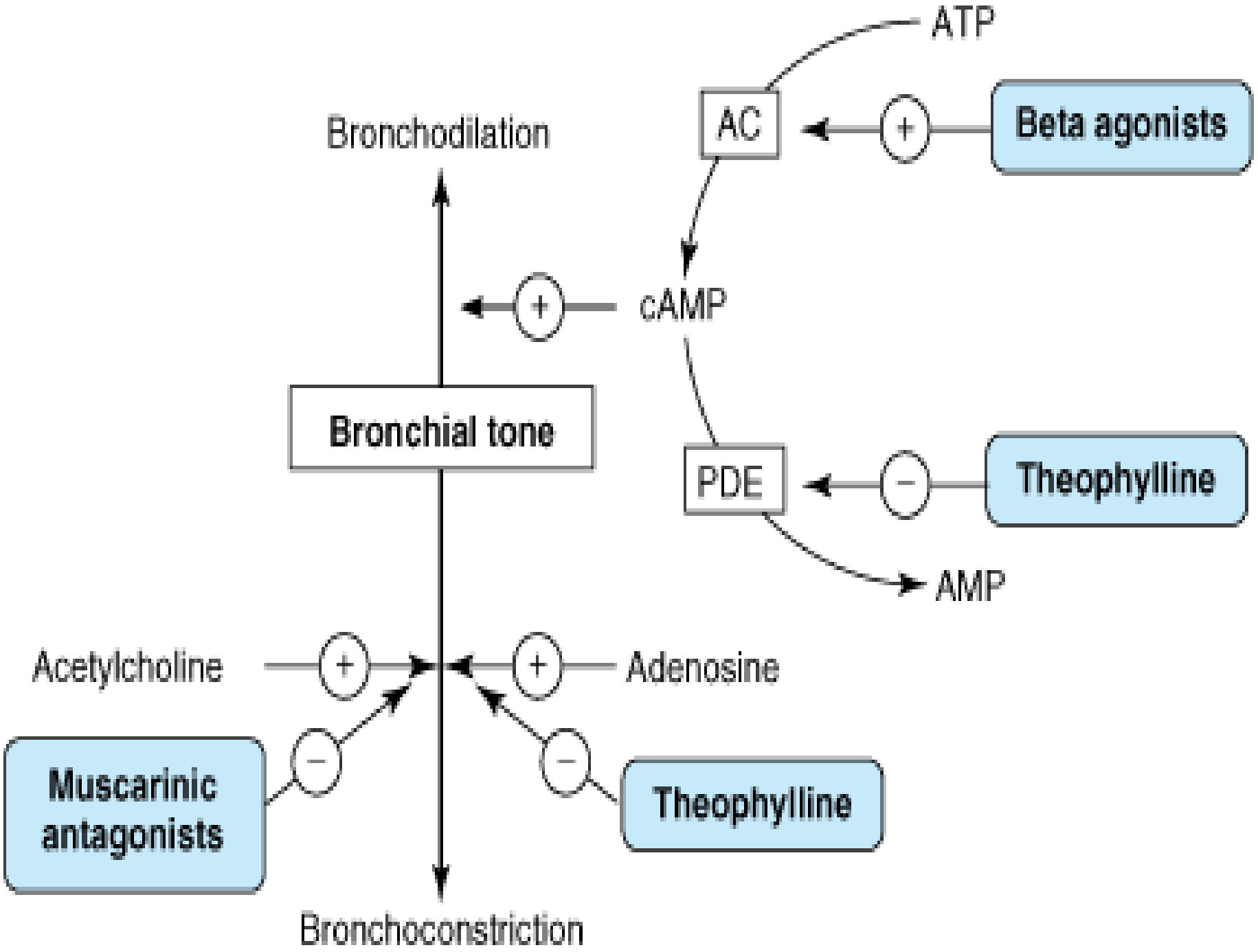
Metaproterenol



Salmeterol

BRONCHODILATORS
SYMPATHOMIMETICS

- epinephrine— α, β
- isoproterinol—β1 , β2
- ephedrine α , β
- terbutaline– β2
- albutirol,salbutamol__β2
- metaproterinol__ β2
- salmeterol—long acting
- formeterol---long acting


ATP
AC
Beta agonists
Bronchodilation
cAMP
Bronchial tone
PDE
Theophylline
AMP
Acetylcholine
Adenosine
Muscarinic antagonists
Theophylline
Bronchoconstriction

MECHAMISM

- increase cAMP
- relax airway smooth muscle
- inhibit mediator release from mast cell
- inhibit microvascular leakage
- increase mucociliary transport
- A/E: tachycardia
- sk.muscle tremors

1. MOA of Bronchodilatation

They activate β_2 receptors in airway smooth muscles.

↓

Stimulate adenyl cyclase

↓

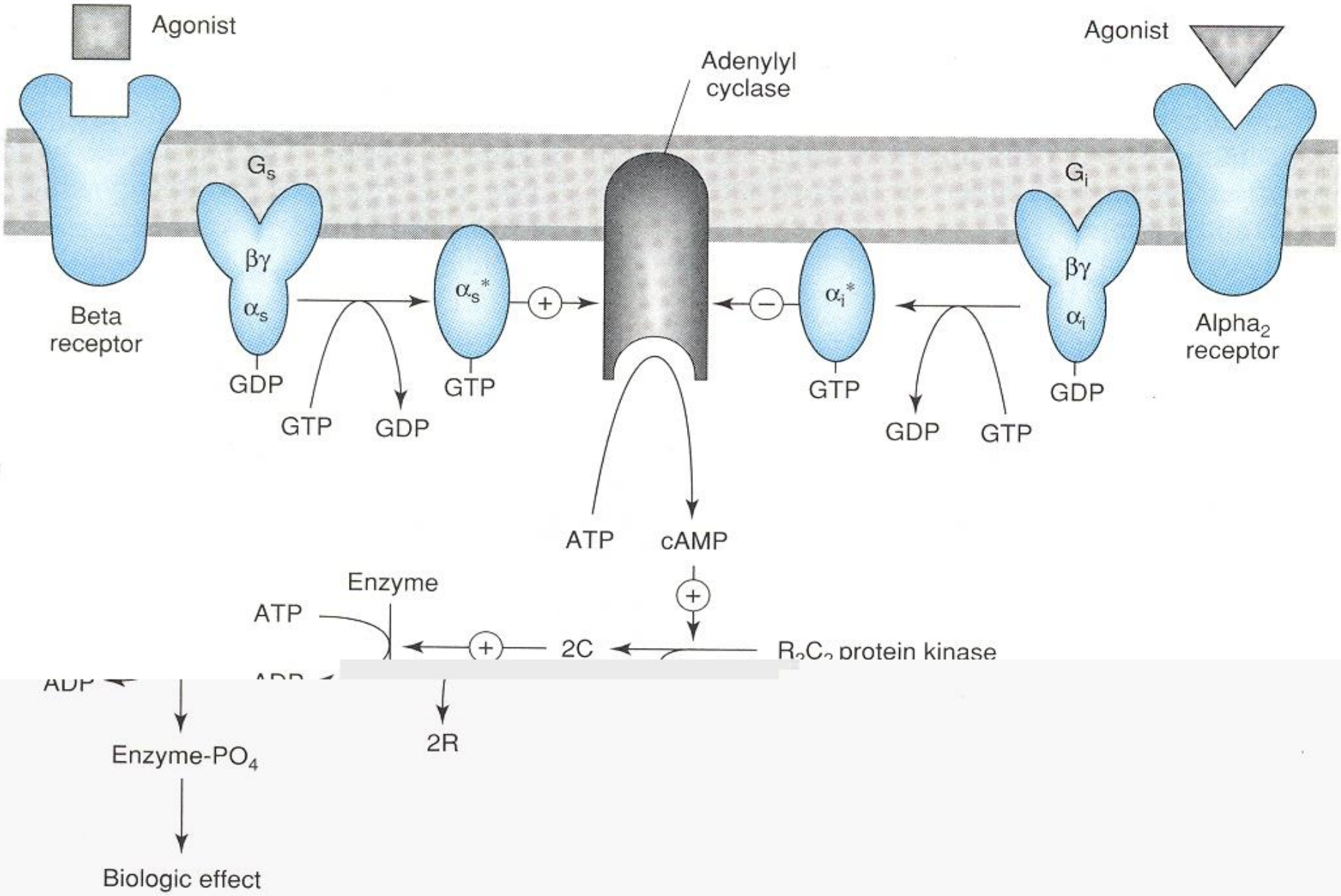
↑ cAMP

↓

↑Rate of inactivation of MLCk --- the enzymes responsible for triggering the interaction of actin & myocin

↓

Relaxation of smooth muscle → Brochodilatation


Agonist
Agonist
Adenylyl cyclase
Beta receptor
G_s
$\beta\gamma$
α_s
GDP
GTP
GDP
α_s^*
GTP
α_i^*
GTP
G_i
$\beta\gamma$
α_i
GDP
GDP
GTP
Alpha$_2$ receptor
ATP
cAMP
Enzyme
ATP
2C
R_2C_2 protein kinase
ADP
2R
Enzyme-PO_4
Biologic effect

B_2 SELECTIVE

MOST WIDELY USED

- selectivety—never 100 %

Tachycardia (direct β1 stimulation)

- Reflexly (due to peripheral vasodilation
- significant no. of β2 receptor in blood vessels)
- inhaler, nebulizer,tablet, injection
- long acting—lipid soluble
- particle size—opt size 2—4 u

They are β_2 selective agonists , little effect on $\beta_1$and α receptors in therapeutic doses, so less adverse effects.

The selectivity is lost at higher doses & adverse effects due to β_1 stimulation may occur

ADVERSE EFFECTS

- sk. muscle tremor
- nervousness
- tachycardia
- weakness (occasionally)
- dec. by starting with low dose

- **hypoximia**
- **tachyphylaxis**
- **cardiac arrhythmia**

Therapeutic uses: β_2 agonists..

most effective, rapidly acting, safe & inexpensive Bronchodilators.

Best delivered by inhalation.

1. **Bronchial Asthma:** Best delivered by inhalation as metered-dose inhalers / nebulizers

i. For therapy of acute episodes ---- short acting β_2 agonists (Salbutamol , Metaproterenol, Terbutaline) are the drug of choice (

- Short acting β_2 agonists are given alone for mild intermittent asthma on a a as-needed basis.
- In severe cases: They are combined with Corticosteroids/ LT receptor antagonists

Max. Bronchodilatation occurs in 15 – 30 min. **DOA:** 4-6hrs

ii. For maintenance treatment of bronchial asthma:

Long acting β_2 selective agonists; Salmeterol, Formoterol are used.

- **DOA:** 12 hrs or more ----- highly lipid soluble dissolve in smooth muscle cell membranes in high concentration .

- they are not recommended as monotherapy for asthma, so combined with LT receptor blockers / inhaled glucocorticoids

- β_2 selective agonists are synergistic with inhaled corticosteroids to improve asthma control.

iii. **Acute Severe Bronchial Asthma / Status Asthmaticus**
-- short acting β_2 selective agonists like Albuterol by inhalation; along with other drugs

Terbutaline may be given by S/c injection.

2. **Chronic obstructive pulmonary disease (COPD).** β_2 selective agonists reverse brochoconstriction.

3. **Premature labor (DOC--- Ritodrine) to delay labor for 24-48 hrs– by slow I/V infusion.**


Ventolin™
Inhaler
Salbutamol
CFC Free
Salbutamol BP 0.1 mg per dose
200 doses
GlaxoSmith


NDC 42023-159-25
Adrenalin®
(epinephrine
injection, USP)
1 mg/mL
1:1000
1 mL Solution in a 3 mL
Single-Use Vial

Advantages of Inhalation

- Self administration.
- The greatest effect in bronchi.
- Least systemic effects or toxicity.
- Rapid OOA.
- Less doses are required.

Epinephrine:

effective & rapid acting bronchodilator.

- Because it stimulates both β_1, β_2 & α receptors , only used in severe acute asthma / status asthmaticus

- 0.4 ml of 1:1000 sol. by S/C injection.
- Or by inhalation 320 µg per puff.
-
- Max. effect after inhalation in 15 min & DOA: 60-90 min.

Adverse effects:

As it activates β_1, β_2 & α receptors, produces following effects:

- Tachycardia, arrhythmias & worsening of angina.

Isoproteresnol:

- Synthetic catecholamine
- Potent bronchodilator
- Stimulates both β_1, β_2 receptors
- Given by inhalation
- Maximum bronchodilation in 5minutes.
- DOA: 60-90min
- A/E: cardiac arrhythmias- increased mortality rate, so β2 selective agonists are used.

METHYLXANTHINES
RELIEVERS

- THEOPHYLLINE
- AMINOPHYLLINE
- OXTRIPHYLLINE
- SLOW RELEASE PREP…
  SLO-PHYLLIN, THEO-DUR.


10 mL Single-dose
Aminophylline
Injection, USP
250 mg (25 mg/mL)
℞ only
Protect from light.
DO NOT USE IF CRYSTALS HAVE SEPARATED FROM SOLUTION.
HOSPIRA, INC., LAKE FOREST, IL 60045 USA

METHYLXANTHINES

- theophylilne_**tea**
- theobromine_cocoa
- caffeine_coffee
- aminophylline;
  theophyline + ethylenediamine
- **kinetics:**
- well abs. from git
- metabolised in liver
- demethylated xanthine-ex in ur.

MECHANISM OF ACTION

- inhibition of phosphodiesrase PDE4 – inc. camp
- inhibition of adenosine receptor- contraction Of s.m & histamine release
- antiinflammatory action-- inhibit release of cytokines and chemokines thru PDE4 (enhancement of histone deacetylation)

ORGAN SYSTEM EFFECTS

- **CNS**
- deferal of fatigue , alertness nervousness , insomnia,tremor, convulsion
- **CVS**
- + inotropic +chronotropic tachycardia ,arrhythmia, inc. catecholamine, inc. ca++ impaired seq.of ca++
- **BLOOD VESSEL** inc. bp

ORGAN SYSTEM EFFECTS

- **GIT**
- stimulation of gast. sec. & enz.
- **KIDNEY**
- weak diuretic action
- **RESPIRATORY SYSTEM**
- direct- bronchdilation
- inhibit histamine release-lung tissue
- **SK. MUSCLE**—strengthen
- improve diaphragm performance

ADVERSE EFFECTS

- **LOW THERAPEUTIC INDEX**
- **GIT**
- anorexia. nausea, vomiting, abdominal discomfort
- **CNS**
- headache,anxiety,
- tremor,convulsion,
- **CVS**
- palpitation, arrhythmia

ADVANTAGES & DISADVANTAGES

- INEXPENSIVE
- ORAL
- SOLE MAINTENANCE THERAPY

- low ther…index
- serum level monitoring
- minor effect– troublesome-- insomnia
- toxic intake

Drug Interactions of Methylxanthines :.

Enzyme inhibitors slow metabolism ↑ plasma levels; Important because of low therapeutic index.

- Oral contraceptives, Cimetidine, Erythromycin , Ciprofloxacin , calcium channel blockers.

Enzyme inducers accelerate metabolism, ↓ plasma levels

- Phenytoin, Barbiturates, Rifampin, Cigarette smoke—

Precautions for use of Methylxanthines :

- Hepatic & cardiac disease.
- Elderly patients.
- Epilepsy
- Breast feeding.

PARASYMPATHOLYTICS
RELIEVERS

- ATROPINE SULPHATE
- IPRATROPIUM BROMIDE
- TIOTROPIUM

MUSCRINIC ANTAGONIST

- datura stamonium leaf— for 100 of years
- mechanism
- competitive antagonism at muscrinic receptors.
- block contraction of smooth muscle
- dec. secretion of muc**us**
- **response related to acetylycholine is inhibited**
- response varies in individual

ATROPINE

- **USE**
- I/v ; much low dose
- aerosol ; more selective
- inc. caliber equal to β2 agonist
- **adverse effects**
- dry mouth__local effect
- systemic effects__large dose

IPRATROPIUM BROMIDE

- new
- more effective
- quaternary ammonium compound
- derivative of atropine
- poorly absorbed
- devoid of CNS effects
- effective bronchodilation
- **tiotropium**
- **long acting,improve copd**
- **alternative to long β2 agoist.**

USES

- where β agonists are contraindicated
- in combination with b agonist, more effective.
- prolong & greater effect.
- psychogenic asthma
- pts. on β_blockers
- slower effect (1-2) hrs. peak act.
- suitable for prophylaxis
- individual variation in response

ADVERSE EFFECTS

- dry mouth
- nausea
- cough
- headache
- dizziness
- nervousness

.

In our 2nd lecture, we have discussed:

Pharmacology of bronchodilators

- Beta agonists
- Methylxanthines
- Anticholinergics

- Today we will discuss all Antiinflammatory drugs including
- Corticosteroids
- Mast cell stabilizers
- Leukotriene blockers
- Anti IgE antibodies

ANTI INFLAMMATORY (*CONTROLLERS*)

CORTICOSTEROID

- **INHALATION**
- beclomethasone
- triamcinolone
- flunisolide
- fluticasone
- budesonide
- mometasone
- ciclesonide

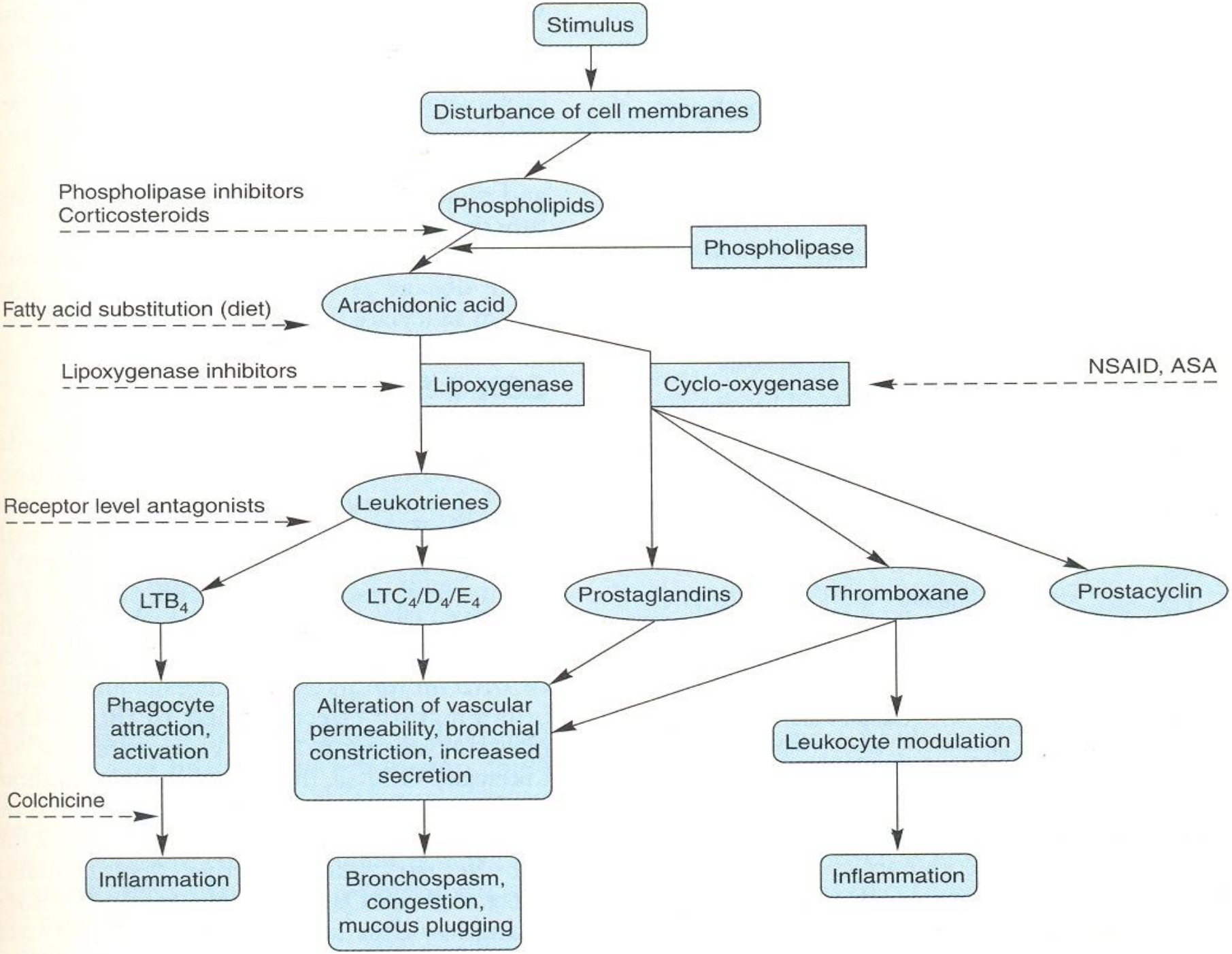
- **ORAL**
- prednisone

- **INJECTABLE**
- methylprednisolone
- hydrocortisone


Onlymyhealth

CORTICOSTEROID (Phospholipase A2inhibitor)

- **inhibit lymphocytic, eosinophilic and mast cell infiltration in mucosa of a..w**
- no direct effect on s. muscle
- antiinflammatory-inhibit cytokine production
- reduce bronchial reactivity
- inc.air way caliber
- dec. frequency of asthma exacerbation
- **partly potentiate β agonist act**


Stimulus
Disturbance of cell membranes
Phospholipase inhibitors
Corticosteroids
Phospholipids
Phospholipase
Fatty acid substitution (diet)
Arachidonic acid
Lipoxygenase inhibitors
Lipoxygenase
Cyclo-oxygenase
NSAID, ASA
Receptor level antagonists
Leukotrienes
LTB4
LTC4/D4/E4
Prostaglandins
Thromboxane
Prostacyclin
Phagocyte attraction, activation
Alteration of vascular permeability, bronchial constriction, increased secretion
Leukocyte modulation
Colchicine
Inflammation
Bronchospasm, congestion, mucous plugging
Inflammation

PREPARATIONS

ORAL

prednisone 30-60 mg

i/v

methyl prednisolone 1mg/kg 6hrly of

HYDROCORTISONE

- **INHALATION**
- beclomethasone
- triamcinolone
- flunisolide
- fluticasone
- budesonide
- mometasone
- ciclesonide
- **LESS SYSTEMIC EFFECTS**

ADVERSE EFFECT

- adrenal suppression
- Cushing sundrome
- Peptic ulcer, hypertension,hyperglycemia
- oropharyngial candidiasis
- hoarseness
- They inc. risk of osteoprosis
- Cataract; glaucoma
- slow rate of growth in children-
- delay puberty
- **ciclesonide—prodrug ,active Site**

CAUTIONS

- **to avoid worsening**

gradual dec. in dose **(tapered)**

- **to avoid adrenal suppression**

early morning after peak of ACTH

- **for nocturnal prevention**

given at late after noon

- **to avoid systemic effect**

inhalars & aerosol

Clinical Use of Glucocorticoid in Bronchial Asthma:-

1. **In chronic severe asthma**:

- If symptoms persists despite bronchodilator therapy , inhaled corticosteroids should be started.

- Combinations of an inhaled glucocorticoid & β_2 agonist in a single inhaler are commonly prescribed:

- Fluticasone & Salmeterol
- Budenoside & Formeterol

- Clinical Use of Glucocorticoids in Bronchial asthma-conti--
- In severe cases, combination of inhaled & oral therapy
- 30-60 mg prednisone daily for 5 days or I/V Methylprednisolone (1mg/kg) 6 hrly.
- After improvement oral dose is gradually ↓ over 7 – 10 days & inhaled corticosteroid continued.

2. In acute severe Asthma:

- I/V Hydrocortisone: 200 – 300 mg I/V

  or

- Methylprednisolone (1mg/kg) 6 hrly.

Followed by oral prednisone / Prednisolone. 0.5mg/ kg every 6 hrs.

Clinical Use of Glucocorticoids in Bronchial asthma:

- They improve all indices of asthma control:
  - Severity of symptoms
  - Tests of airways caliber
  - Bronchial reactivity
  - Frequency of exacerbation
  - Quality of life
- ↓ requirement of β_2 agonists.
- They are not curative.

Advantages of Inhaled Glucocorticoids

- Self administration.
- Rapid OOA.
- Less doses are required.
- The greatest effect in bronchi.
- Least systemic effects or toxicity
- Better effects when used with spacers

A spacer is a large-volume chamber attached to a metered-dose inhaler.

Spacers ↓ deposition of drug in mouth caused by improper inhaler technique .

Spacer:

- The chamber ↓ velocity of aerosol before entering the mouth, allowing large drug particles to be deposited in the device.

- The smaller, higher-velocity drug particles are more likely to reach the target airway tissue. Minimize adrenal suppression by ↓ glucocorticoid deposition in oropharynx.

- Improve delivery of drug, are advised for virtually all pts.

especially children < 5 yrs & elderly -- who may have difficulty in using inhaler.

- Regular washing and / or rinsing of spacers ↓ risk of bacterial or fungal growth inducing an asthma attack.

CROMOLYN & NEDOCROMIL

- only prophylactic use
- no effect on air way muscle
- ineffective in bronchospasm
- poor GI absorption
- by inhalation; especially in children
- microfine powder
- aerosolized sol.
- ex. unchanged in urine

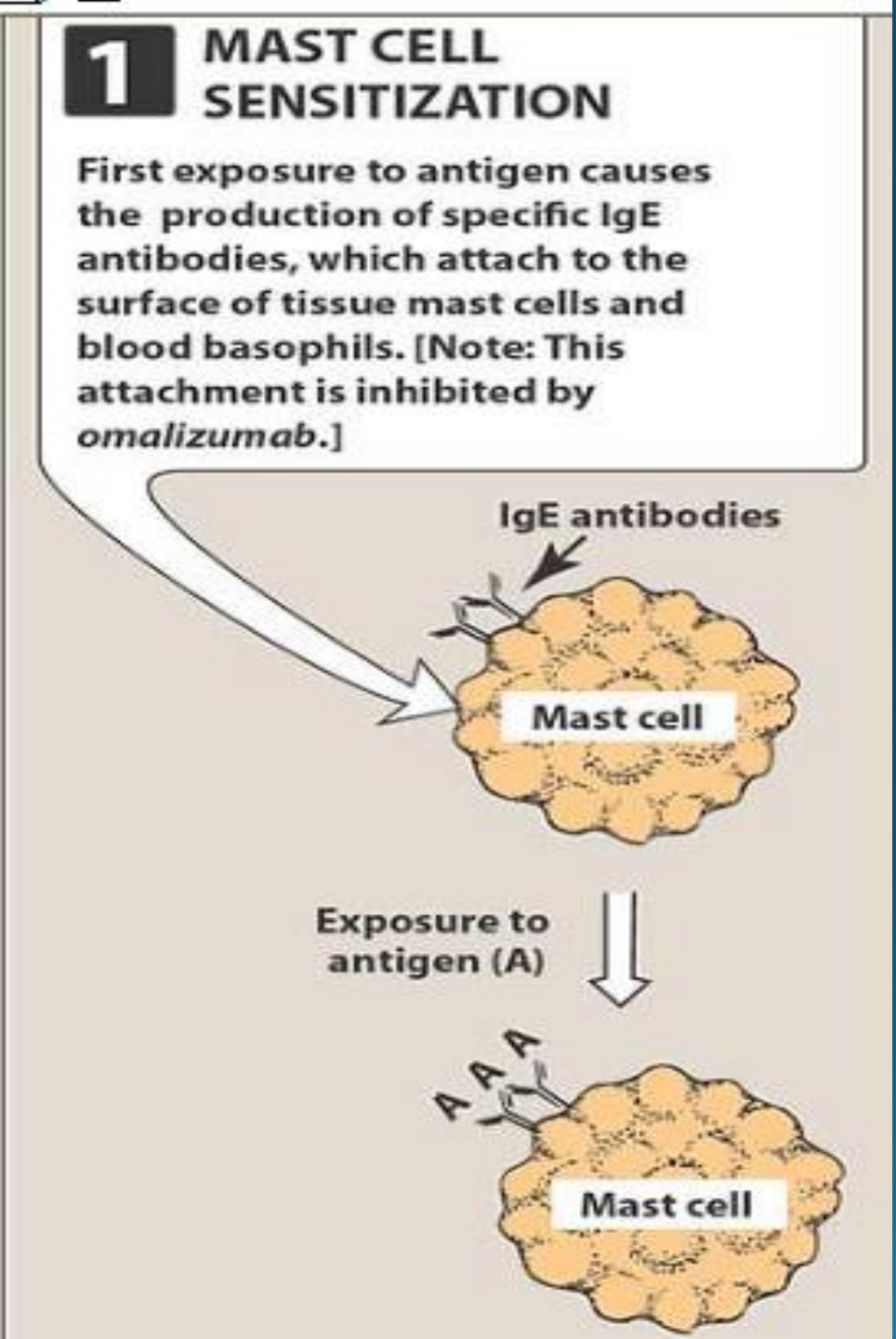
- Little toxicity
- Not potent

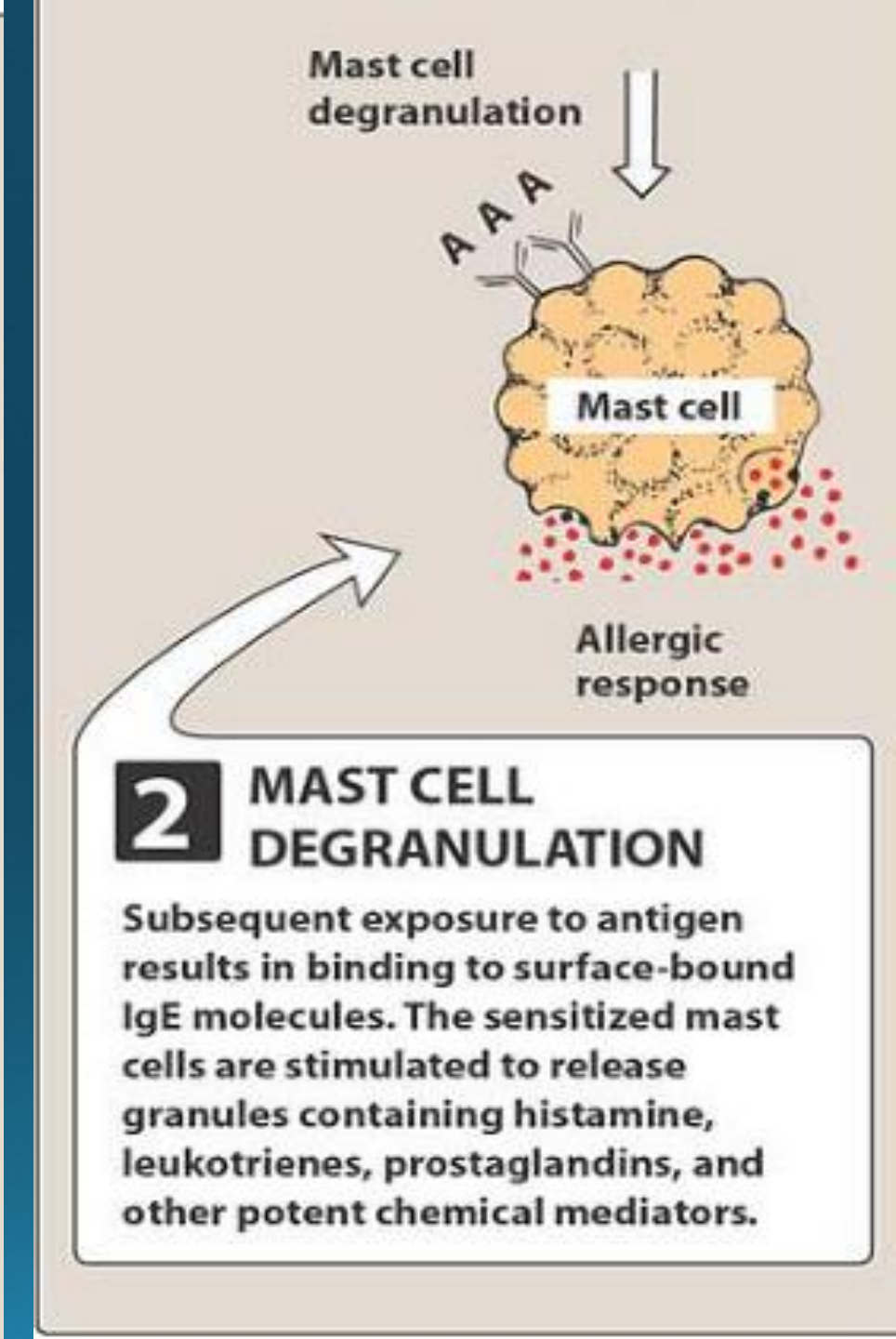
Clinical uses

- Allergic rhinoconjuctivitis
- Systemic mastocytosis

1 MAST CELL SENSITIZATION

First exposure to antigen causes the production of specific IgE antibodies, which attach to the surface of tissue mast cells and blood basophils. [Note: This attachment is inhibited by *omalizumab*.]





2 MAST CELL DEGRANULATION

Subsequent exposure to antigen results in binding to surface-bound IgE molecules. The sensitized mast cells are stimulated to release granules containing histamine, leukotrienes, prostaglandins, and other potent chemical mediators.

LEUKOTRIENE PATHWAY INHIBITORS *CONTROLLERS*

- ZAFIRLUKAST
- MONTELUKAST
- ZILEUTON

LEUKOTRIENE ANTAGONISTS

LIPOXYGENASE INHIBITORS

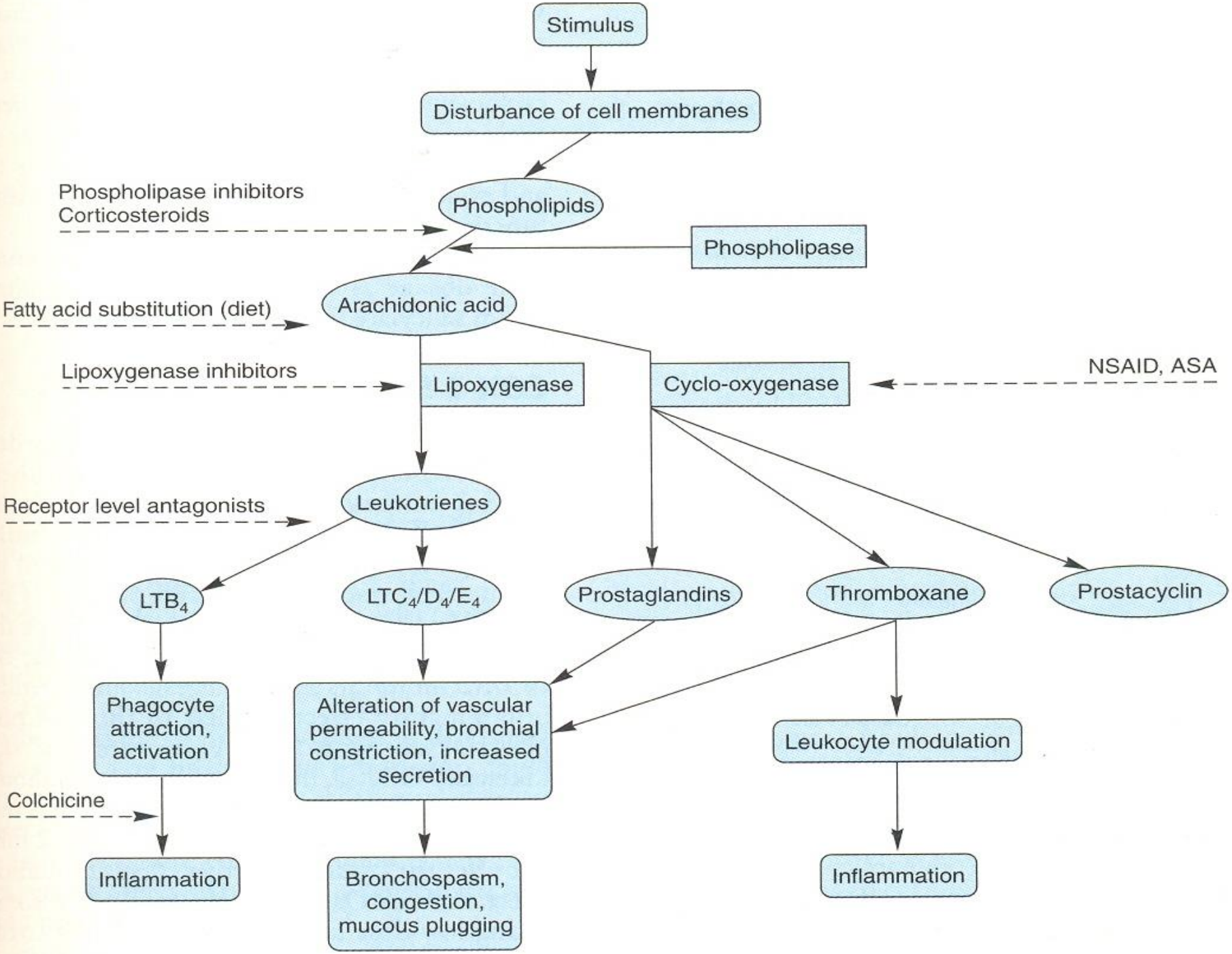
ZILEUTON

RECEPTOR BLOCKERS

ZAFIRLUKAST
MONTELUKAST

LEUKOTRIENE PATHWAY INHIBITORS

- arachidonic acid----------_leukotriene by 5–lipoxygenase in eosinophil, mast cell, macrophages and basophil
- **LTB4_**
- neutrophil chemoattractant
- **LTC4**
- **LTD4**
- bronchoconstriction
- inc. br. reactivity
- mucosal edema
- mucus hypersecretion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Prostaglandins
Thromboxane
Prostacyclin
Phagocyte attraction, activation
Alteration of vascular permeability, bronchial constriction, increased secretion
Leukocyte modulation
Colchicine
Inflammation
Bronchospasm, congestion, mucous plugging
Inflammation

MECHANISM

- **ZAFIRLUKAST**
- **MONTELUKAST**

LTD4 receptor antagonist

- **ZILEUTON**

5—lipoxygenase inhibitor

prevent synthesis

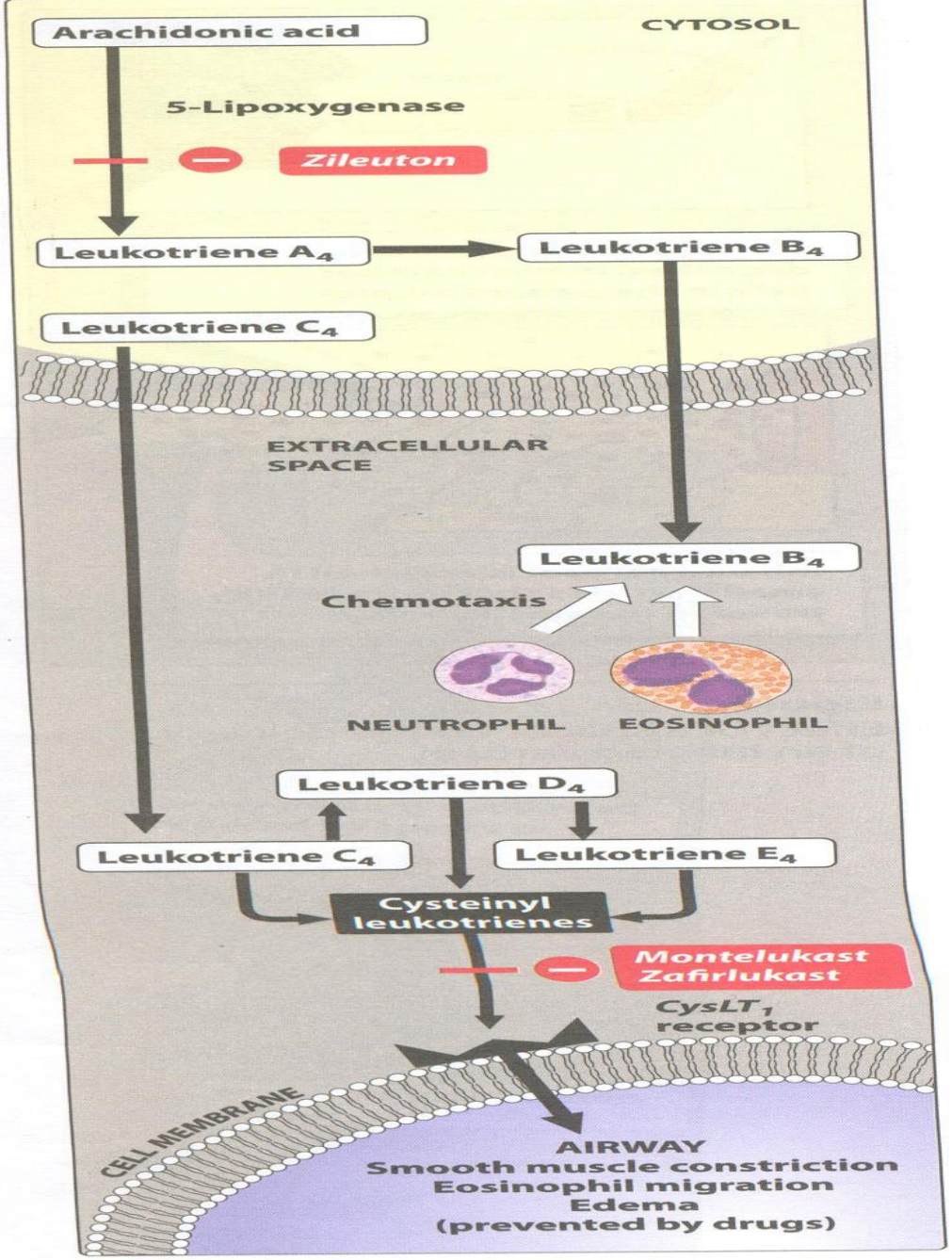
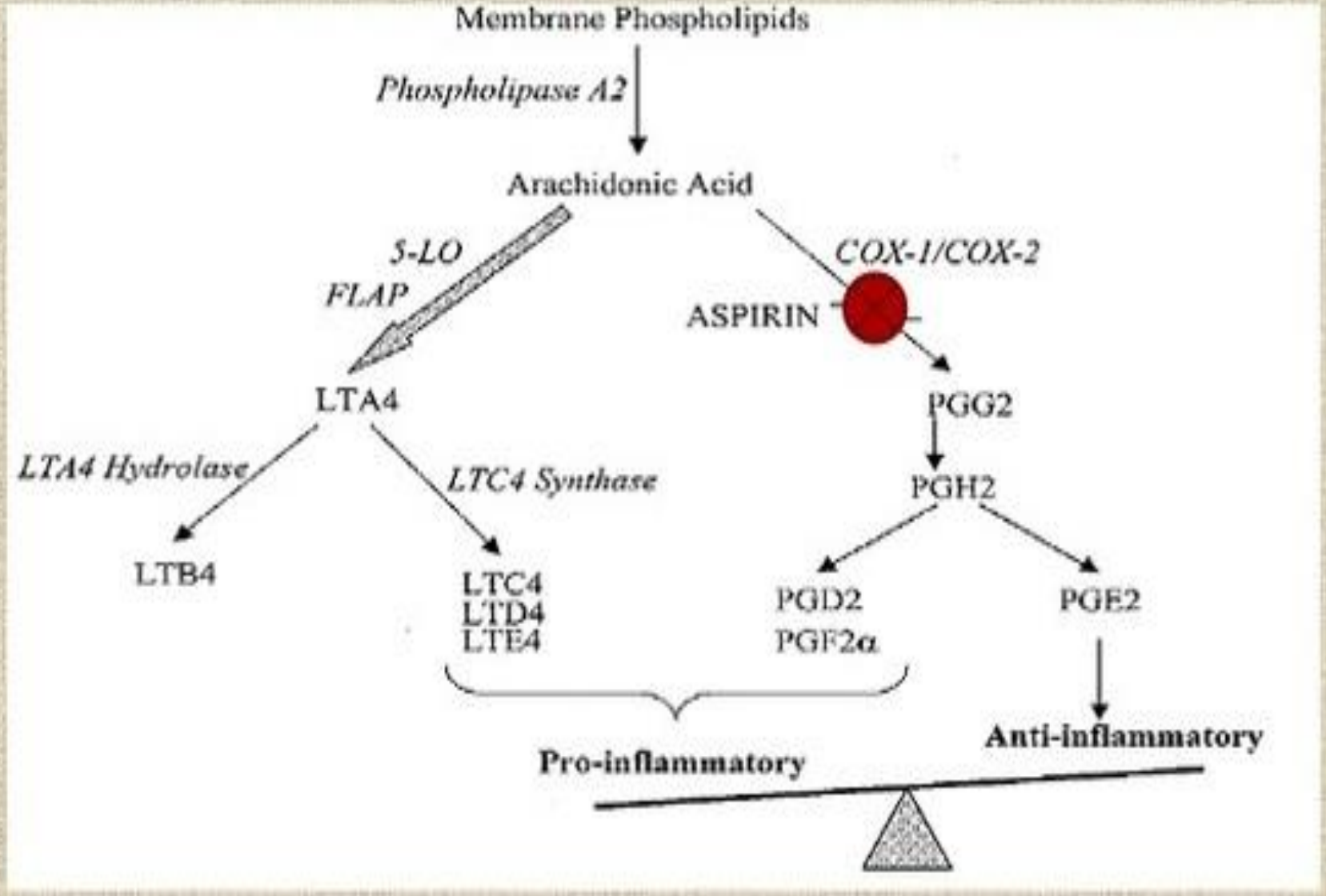


Figure 27.6
Sites of action of leukotriene-modifying drugs. $CysLT_1$ = cysteinyl

ADVERSE EFFECTS

- **minor avoided by b 2 inhalation**
- throat irritation, mouth dryness,
- **serious**
- reversible dermititis, myositis gastroenteritis
- **rare**
- pul. infiltration, anaphylaxis

Reason for Aspirin induced Asthma



ADVERSE EFFECTS

- monteukast---most prescribed , once a day ,no relation to meal

- zafilukast & monteleukast
- appear to be safe

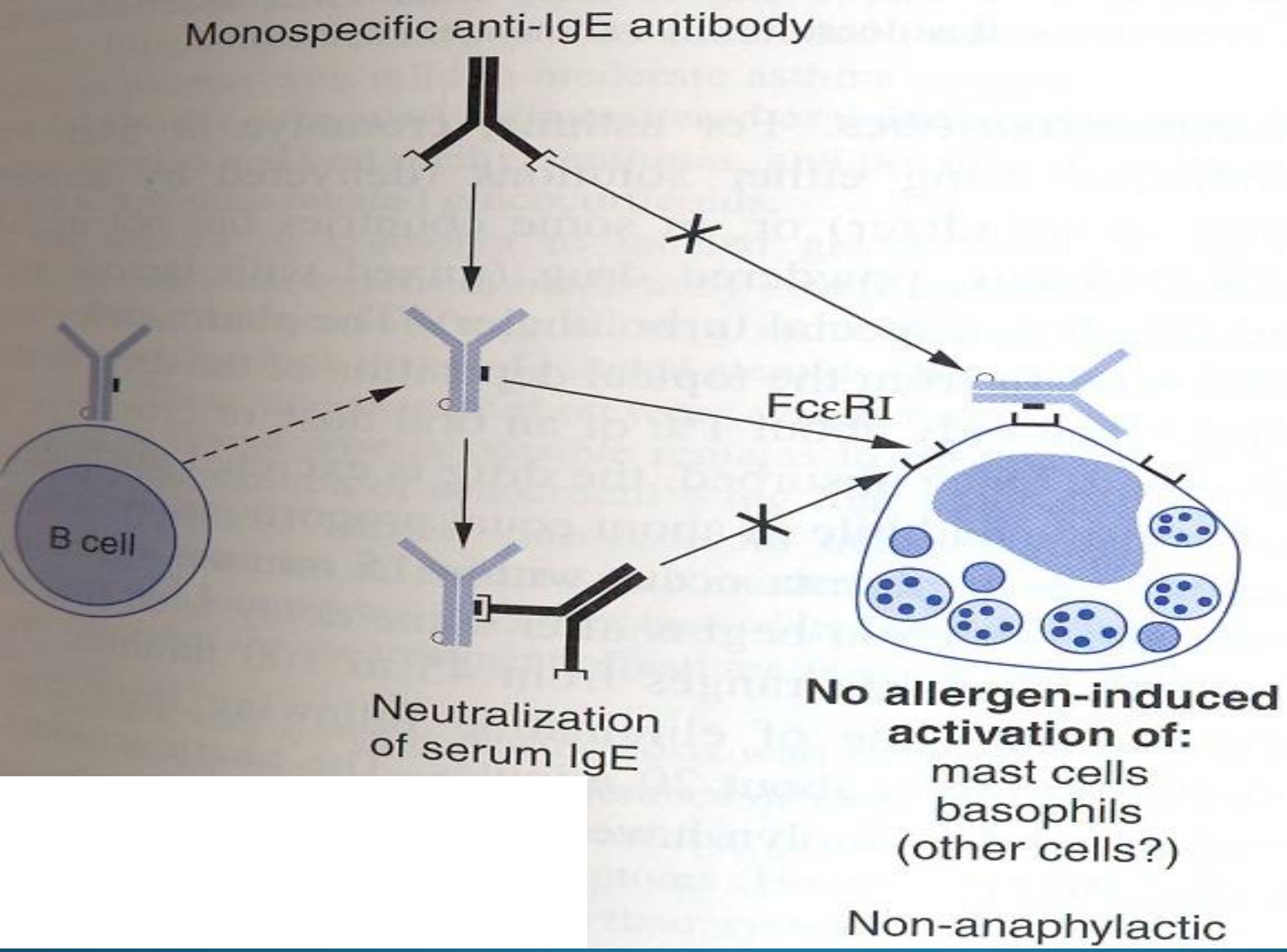
- zileuton ---less prescribed
- frequent dosage
- occasional liver toxicity

USES

- effective
- less than corticosteroids
- variable response___trial
- exercise
- antigen challenge
- aspirin induced asthma
- montelukast-- approved for as young as 6yr.
- given orally

ANTI-IgE MONOCLONAL ANTIBODIES

- **OMALIZUMAB**
- **MECHANISM**
- inhibit binding of IgE to mast cell
- not allow activation of already bound IgE
- no mast cell degranulation
- may inhibit IgE synthesis—b.lymphocytes


Monospecific anti-IgE antibody
B cell
FcεRI
Neutralization
of serum IgE
No allergen-induced
activation of:
mast cells
basophils
(other cells?)
Non-anaphylactic

ADVANTAGES

- decrease asthma severity
- Decrease steroid requirement
- improve symptoms of seasonal & non seasonal all. rhinitis
- **dec. hospitalization**
- **high cost.**
- **i/v or s/c preparation**

ACUTE MODERATE

- SIMILAR DRUGS

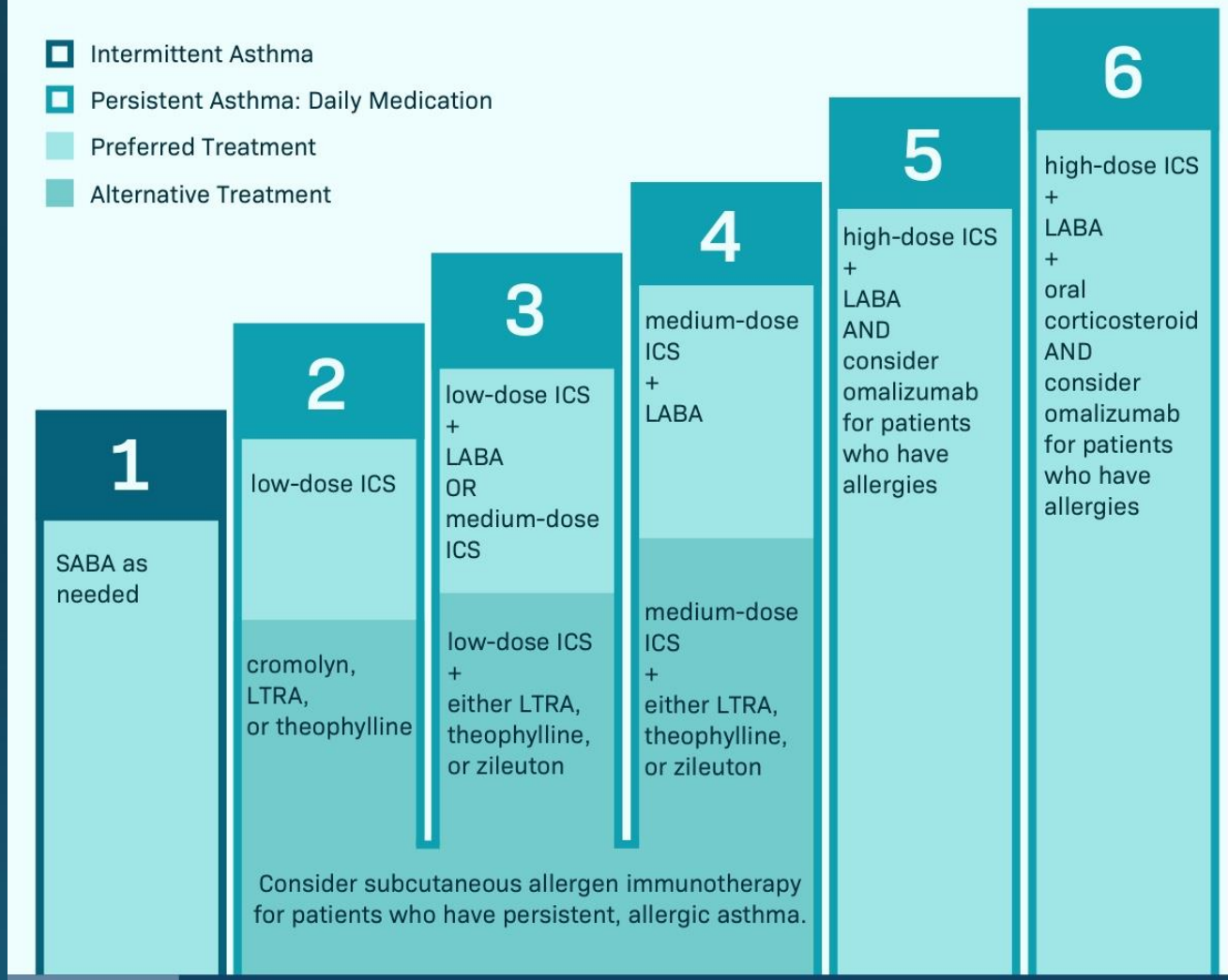
- **ACUTE MILD**
- salbutamol nebulization
- aminophyline i/v or
- epinephrine s/c

ACUTE SEVERE Br. ASTHMA

- close monitoring
- o2 inhalation
- albuterol nebulization,continue
- epinephrine s/c
- hydrocortisone i/v 6 hourly
- aminophyline infusion (slow)
- fluid & electrolyte balance
- blood gases , cardiac function
- endotracheal intubation_
- antibiotics
- mechanical ventilation, if resp. failure

CLASSIFICATION	BRONCHO-CONSTRICTIVE EPISODES	RESULTS OF PEAK FLOW OR SPIROMETRY	LONG-TERM CONTROL	QUICK RELIEF OF SYMPTOMS
Mild intermittent	Less than two per week	Near normal*	No daily medication	Short-acting β_2 agonist
Mild persistent	More than two per week	Near normal*	Low-dose inhaled corticosteroids	Short-acting β_2 agonist
Moderate persistent	Daily	60 to 80 percent of normal	Low- to medium-dose inhaled corticosteroids and a long-acting β_2 agonist	Short-acting β_2 agonist
Severe persistent	Continual	Less than 60 percent of normal	High-dose inhaled corticosteroids and a long-acting β_2 agonist	Short-acting β_2 agonist

Stepwise Approach For Ages 12+



STEPWISE APPROACH - ASTHMA.NET

ANTI-IgE MONOCLONAL ANTIBODIES (OMALIZUMAB)

POSSIBLE FUTURE THERAPIES

- monoclonal antibodies against cytokines
- antagonist of cell adhesion molecule
- protease inhibitors
- immunomodulators
- macrolides for infections


THANK
YOU