Pathologies and drugs of the respiratory apparatus

Prevalence of Asthma

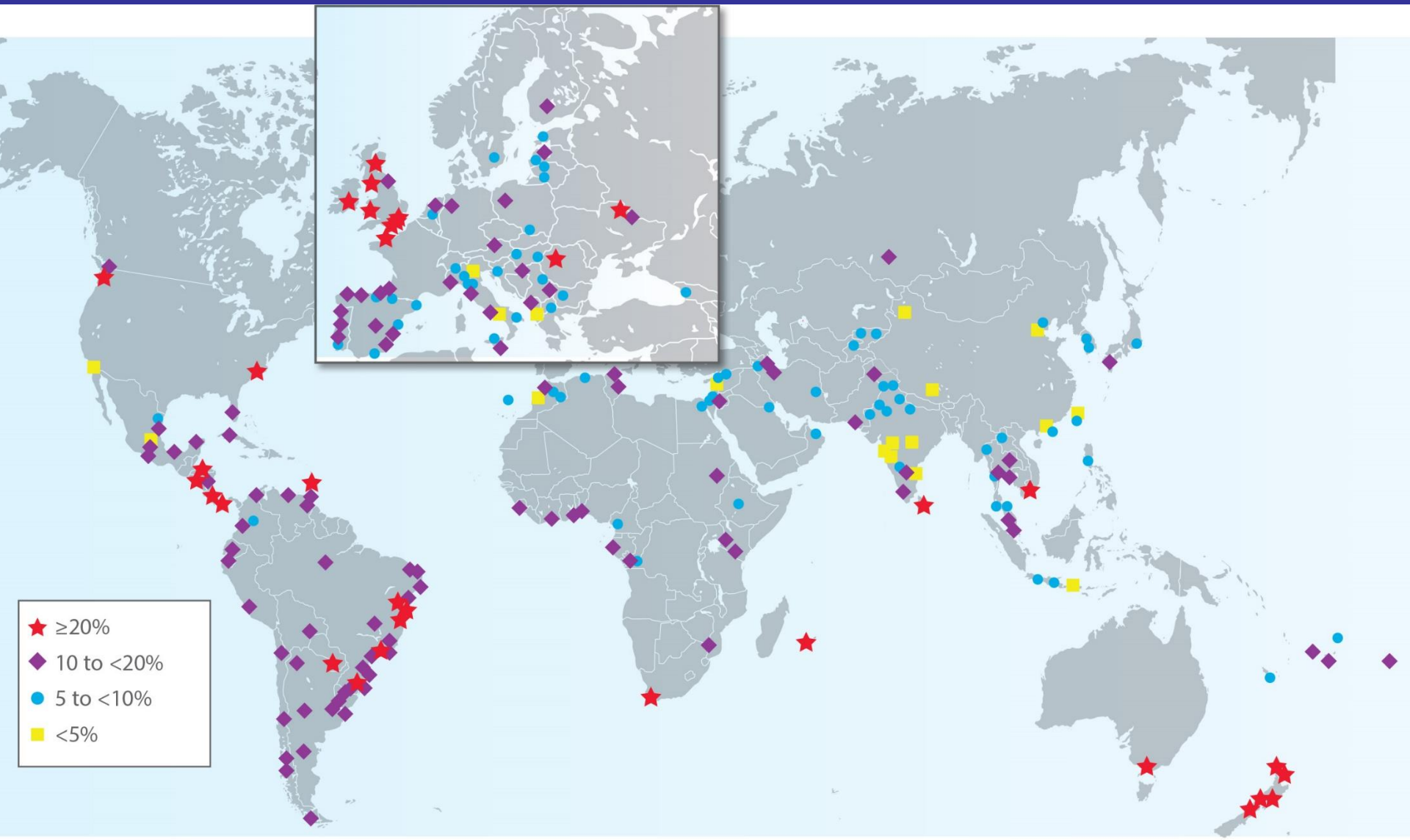


Figure 1: Prevalence of asthma symptoms among 13-14 year olds (ISAAC).

Source: Lai CKW, et al. Thorax 2009.

Physiology of the respiratory apparatus

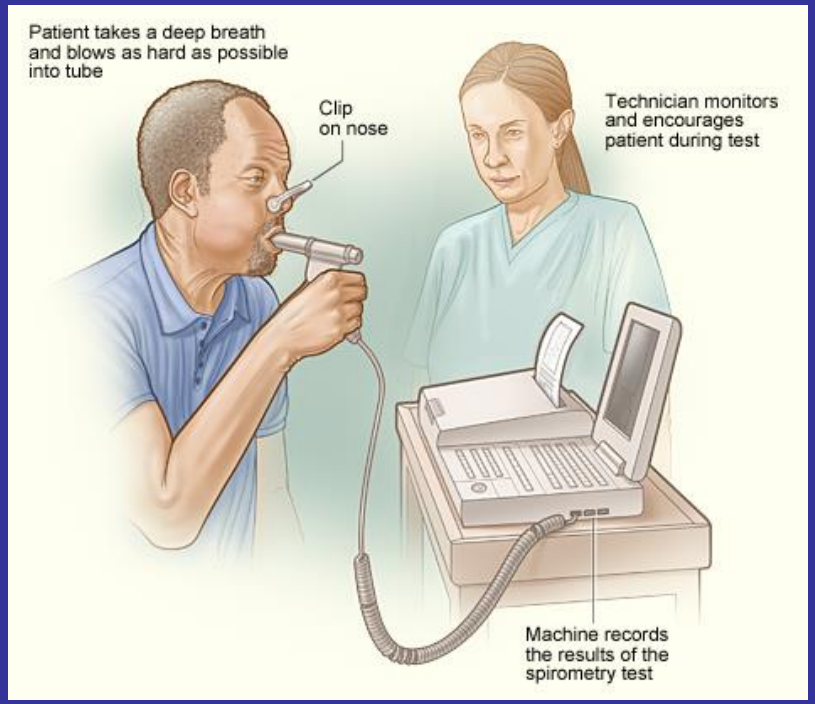
- The parasympathetic nerves mediate bronchial constriction and mucus secretion through an action on muscarinic M_3-receptors.
- Sympathetic nerves innervate blood vessels (causing constriction) and glands (inhibiting secretion), but not airway smooth muscle.
- Circulating adrenaline acts on β_2-adrenoceptors to relax airway smooth muscle.
- The main neurotransmitter causing relaxation of airway smooth muscle is the NANC (non-adrenergic, non-cholinergic) inhibitory transmitter, thought to be nitric oxide.
- NANC excitatory transmitters are peptides released from sensory neurons.

Bronchial Asthma

Bronchial asthma

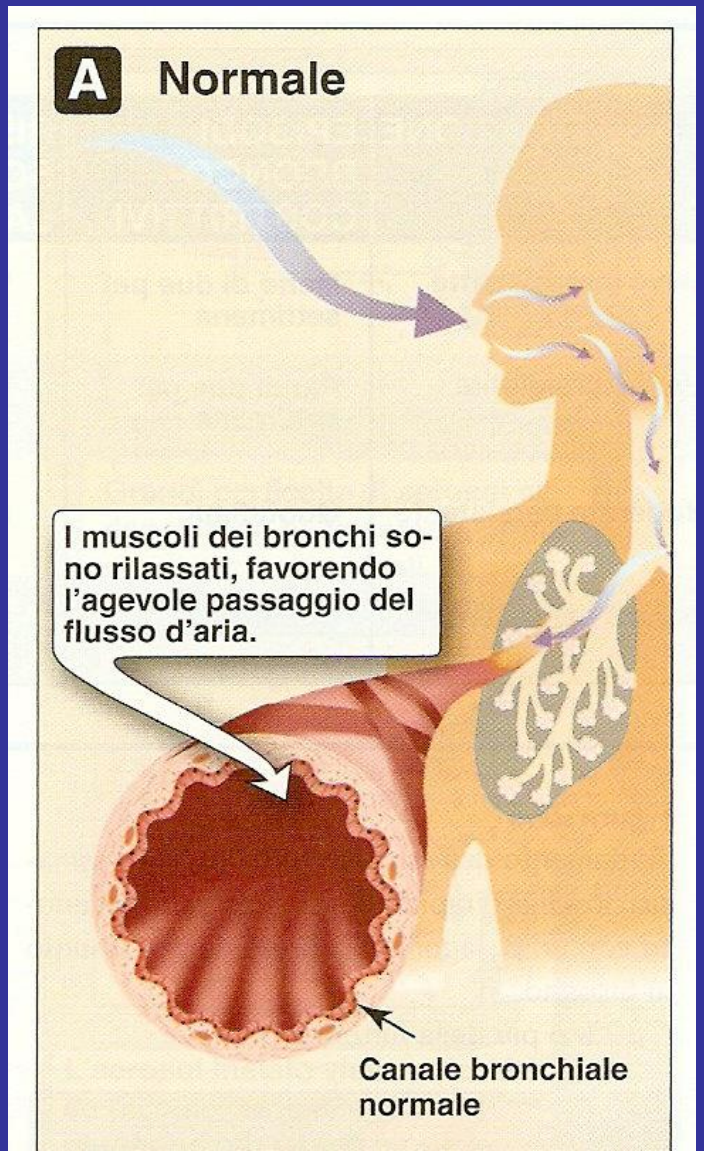
- Asthma is defined as recurrent reversible airway obstruction of airflow through the airway. The asthmatic attack comprises wheezing, cough and difficulty in breathing out; the airways resistance is increased—manifest as a decrease in the 'forced expiratory volume in 1 second' (FEV_1). Severe attacks are life threatening.
- Two characteristic features are:
  - —underlying inflammatory changes in the airways
  - —underlying bronchial hyper-responsiveness, i.e. abnormal sensitivity to stimuli.
- The development of allergic asthma involves exposure of genetically sensitive individuals to allergens; these cause activation of Th2 lymphocytes, which in turn generate cytokines that promote:
  - —differentiation and activation of eosinophils
  - —IgE production and release
  - —expression of IgE receptors on mast cells and eosinophils.
- In many subjects, the asthmatic attack consists of two phases:
  - —an immediate phase on exposure to eliciting agent, consisting mainly of bronchospasm
  - —a later phase consisting of a special type of inflammation in the brochioles comprising: vasodilatation, oedema, mucus secretion and bronchospasm caused by inflammatory mediators released from eosinophils and other cells. Activated, cytokine-releasing Th2 cells have an important role.
- Important mediators include leukotrienes C_4 and D_4, various chemotaxins and chemokines (in both phases) and tissue-damaging eosinophil proteins (delayed phase).

Forced expiratory volume (FEV1)

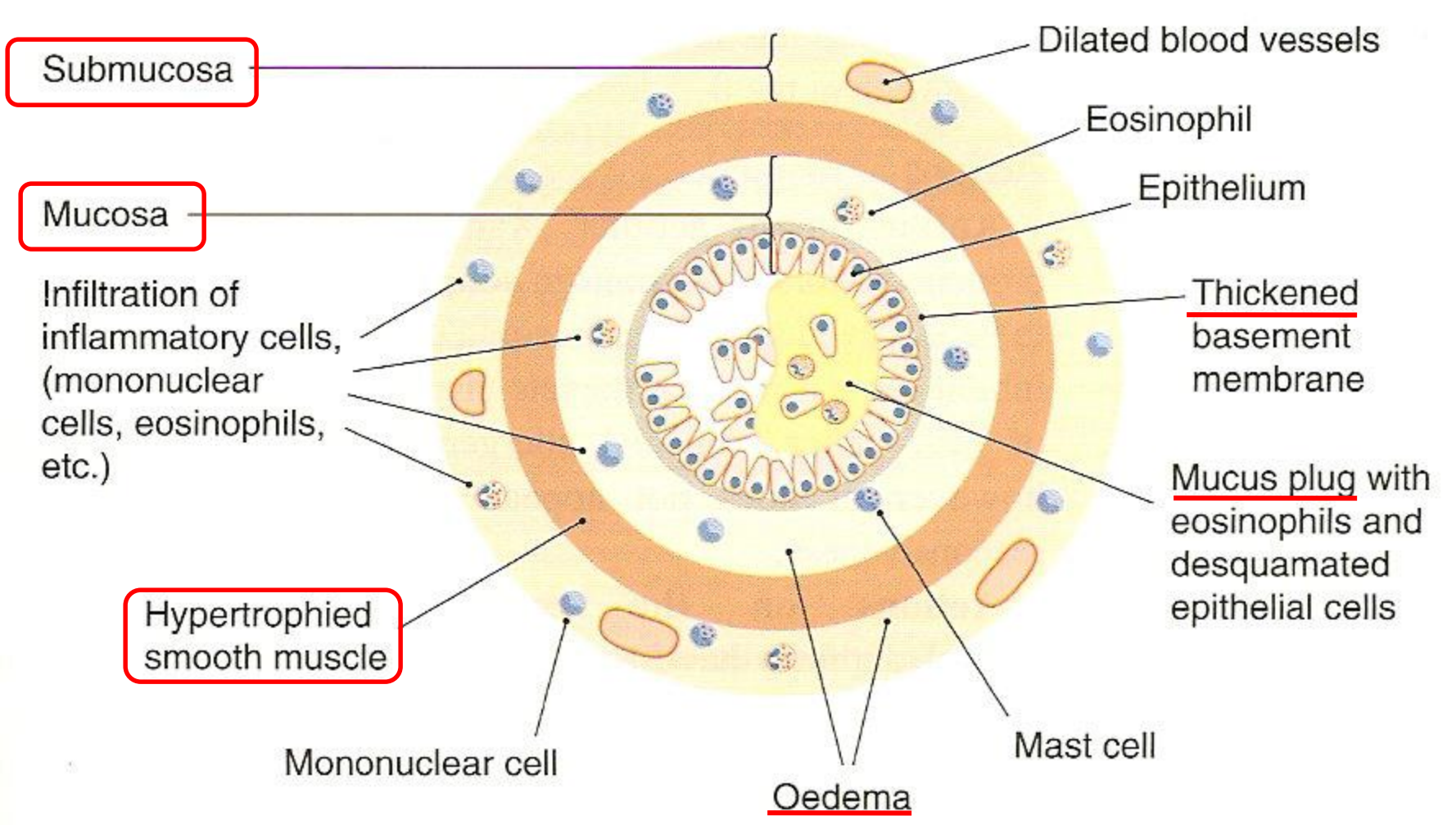


- FEV1 greater than 80% of predicted = normal
- FEV1 60% to 79% of predicted = mild obstruction
- FEV1 40% to 59% of predicted = moderate obstruction
- FEV1 less than 40% of predicted = severe obstruction

Bronchi of a normal and an asthmatic individual



Changes in the bronchioles in chronic asthma



Asthma mechanisms

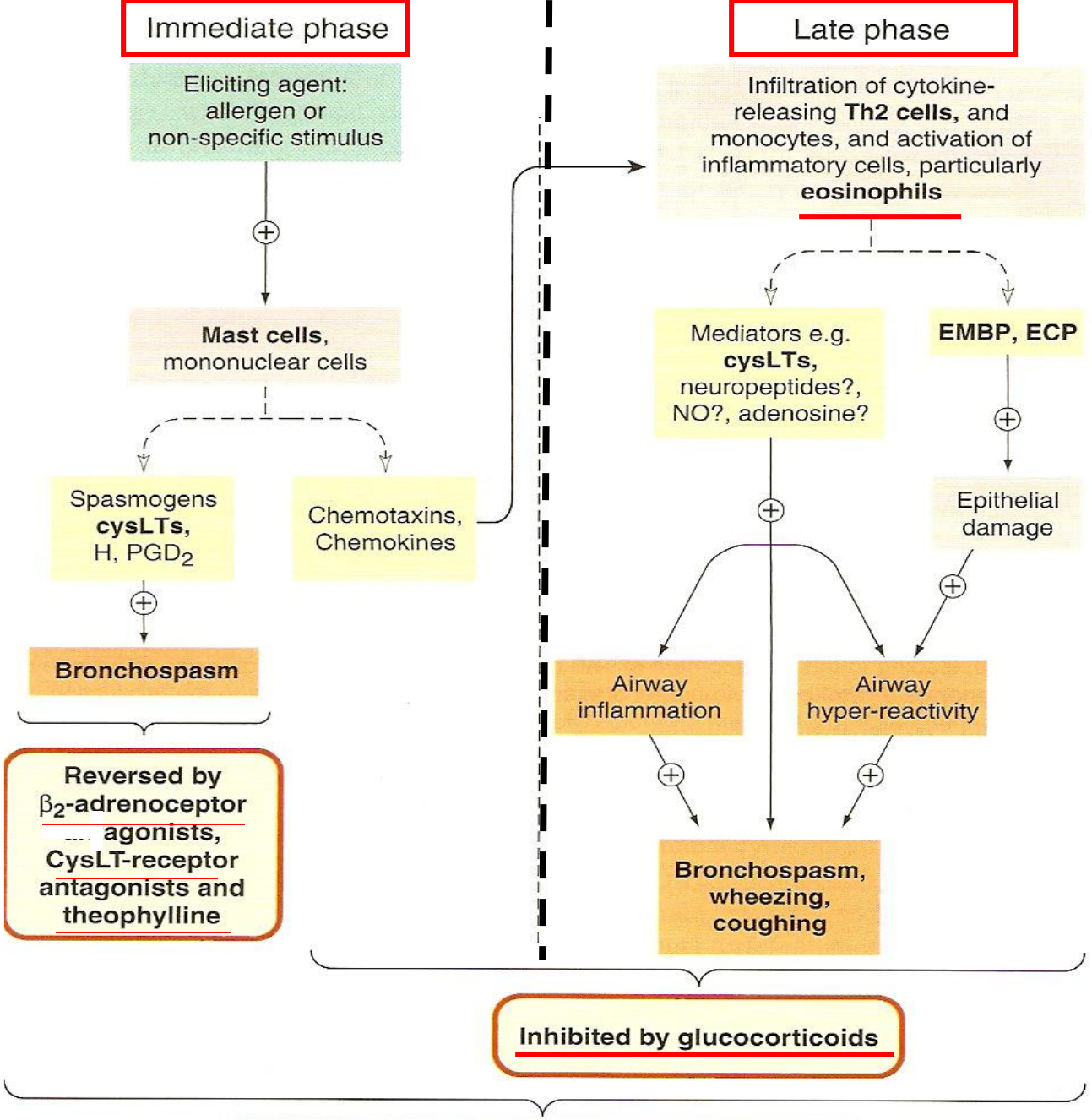
- Inflammation
- T lymphocytes
- Leukotrienes

Drugs

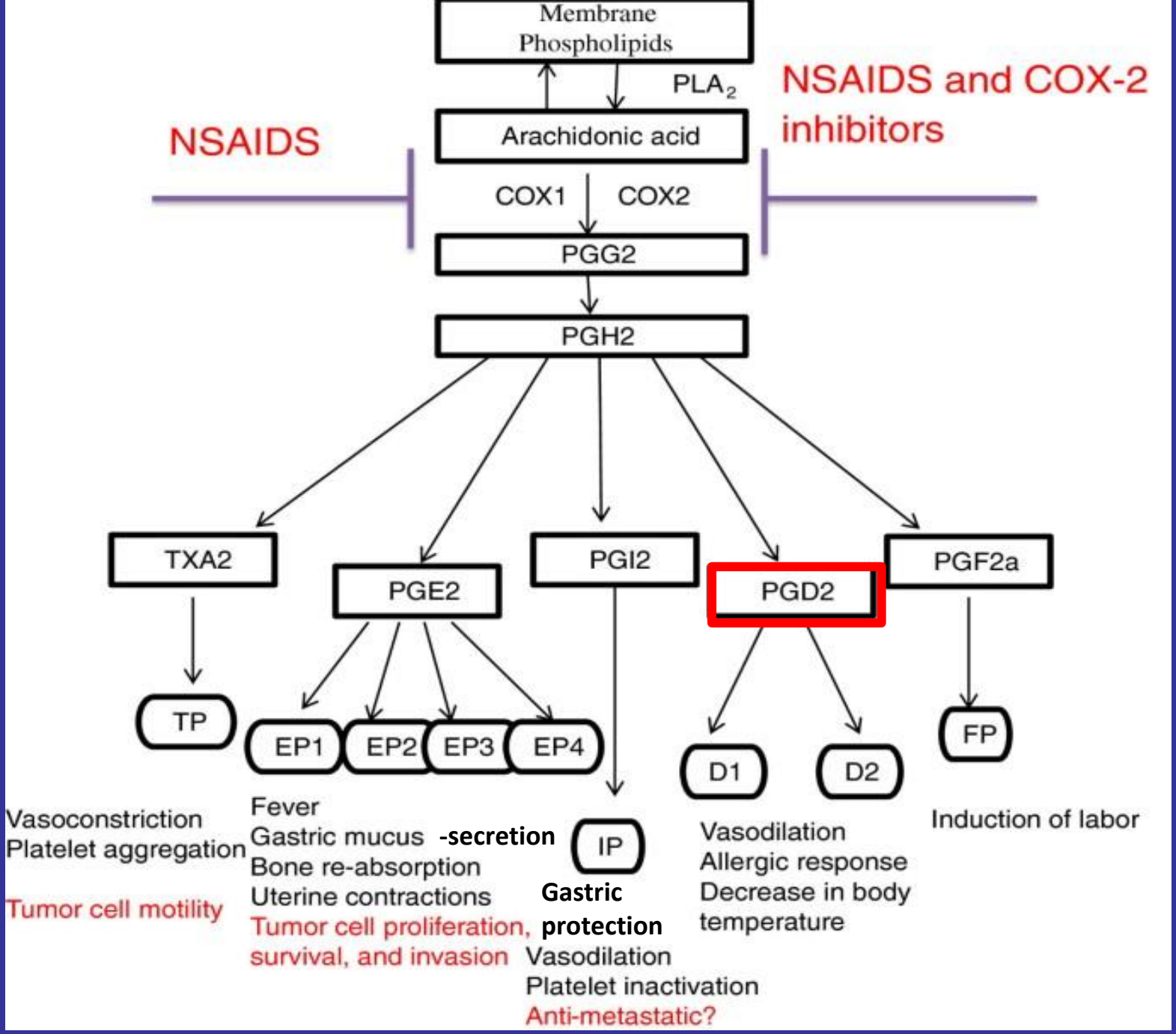
Bronchodilators
Anti-secretory
Anti-leukotrienes
Anti-inflammatory

Respiratory system drugs

Stages of asthma and pharmacological treatment



EMBP = eosinophil major basic protein
ECP = eosinophil cationic protein


Membrane Phospholipids
PLA2
NSAIDS and COX-2 inhibitors
NSAIDS
Arachidonic acid
COX1
COX2
PGG2
PGH2
TXA2
PGE2
PGI2
PGD2
PGF2a
TP
EP1
EP2
EP3
EP4
IP
D1
D2
FP
Vasoconstriction
Platelet aggregation
Tumor cell motility
Fever
Gastric mucus -secretion
Bone re-absorption
Uterine contractions
Tumor cell proliferation, survival, and invasion
Gastric protection
Vasodilation
Platelet inactivation
Anti-metastatic?
Vasodilation
Allergic response
Decrease in body temperature
Induction of labor

Asthma Drugs

Drugs

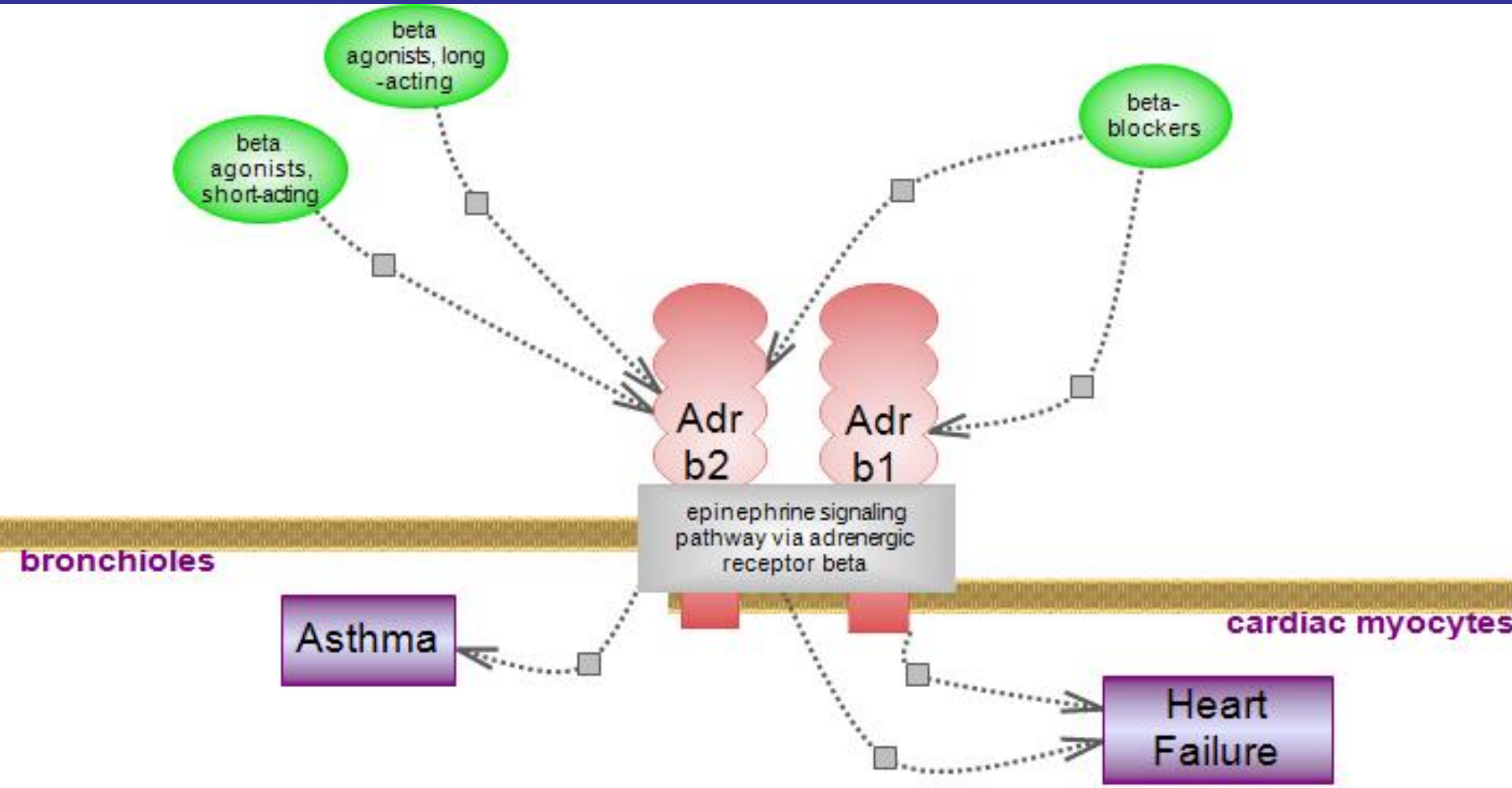
- **Bronchodilators**
- Anti-secretory
- Anti-leukotrienes
- Anti-inflammatory

Antiasthma drugs: bronchodilators

- β_2-Adrenoceptor agonists (e.g. **salbutamol**) are first-line drugs
  - They act as physiological antagonists of the spasmogenic mediators but have little or no effect on the bronchial hyper-reactivity.
  - Salbutamol is given by inhalation; its effects start immediately and last 3–5 hours, and it can also be given by intravenous infusion in status asthmaticus.
  - **Salmeterol** or **formoterol** are given regularly by inhalation; their duration of action is 8–12 hours.
- **Theophylline** (often formulated as **aminophylline)** is a third-line drug for asthma. Theophylline:
  - is a methylxanthine
  - inhibits phosphodiesterase and blocks adenosine receptors
  - has a narrow therapeutic window: unwanted effects include cardiac dysrhythmia, seizures and gastrointestinal disturbances
  - is given intravenously (by ***slow*** infusion) for status asthmaticus, or orally (as a sustained-release preparation) as add-on therapy to inhaled corticosteroids and long-acting β_2 agonists (step 4)
  - is metabolised in the liver by P450; liver dysfunction and viral infections increase its plasma concentration and half-life (normally approximately 12 hours)
  - interacts importantly with other drugs; some (e.g. some antibiotics) increase the half-life of theophylline, others (e.g. anticonvulsants) decrease it.
- Cysteinyl leukotriene receptor antagonists (e.g. **montelukast**) are third-line drugs for asthma. They:
  - competitively antagonise cysteinyl leukotrienes at $CysLT_1$ receptors
  - are used mainly as add-on therapy to inhaled corticosteroids and long-acting β_2 agonists (step 4).

Bronchodilator drugs
β_2-adrenergic

β_2-adrenergic receptors



Clinical use of β_2-adrenoceptor agonists as bronchodilators

- Short-acting drugs (salbutamol or terbutaline, usually by inhalation) to prevent or treat wheeze in patients with reversible obstructive airways disease.
- Salmeterol (long-acting bronchodilator) to prevent bronchospasm (e.g. at night or with exercise) in patients requiring long-term bronchodilator therapy.

β_2-adrenergic *once-daily* : i**ndacaterol, carmoterol, milveterol, vilanterol, olodaterol**

In combination with glucocorticoids

Side Effects

Desensitization

Tremor

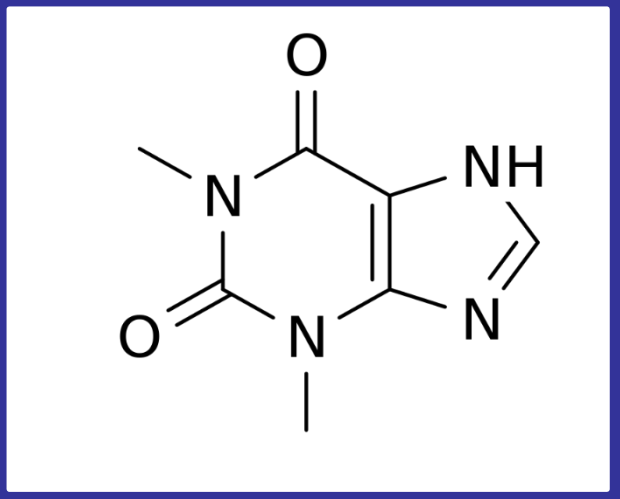
Tachycardia

Arrhythmia

Bronchodilator drugs
Theophylline

Clinical use of theophylline

- As a second-line drug, in additon to steroids, in patients whose asthma does not respond adequately to β_2-adrenoceptor agonists.
- Intravenously in acute severe asthma.
- To reduce symptoms of chronic obstructive pulmonary disease.



Low therapeutic index (heart, intestine)

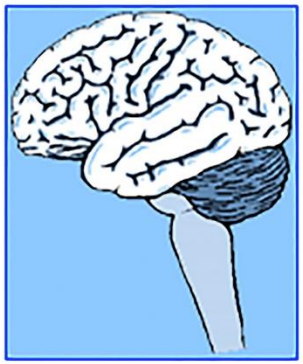
Methylxanthines

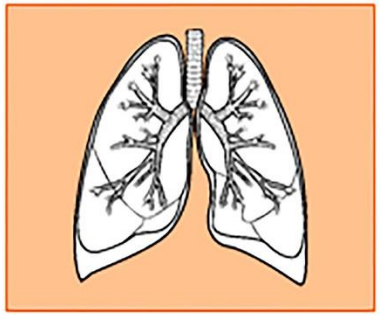
- Theophylline and its derivatives are most commonly used for the treatment of COPD and asthma.
- Caffeine, theophylline and theobromine are naturally occurring xanthine alkaloids which have qualitatively similar actions.

- ***Mechanism of action:***

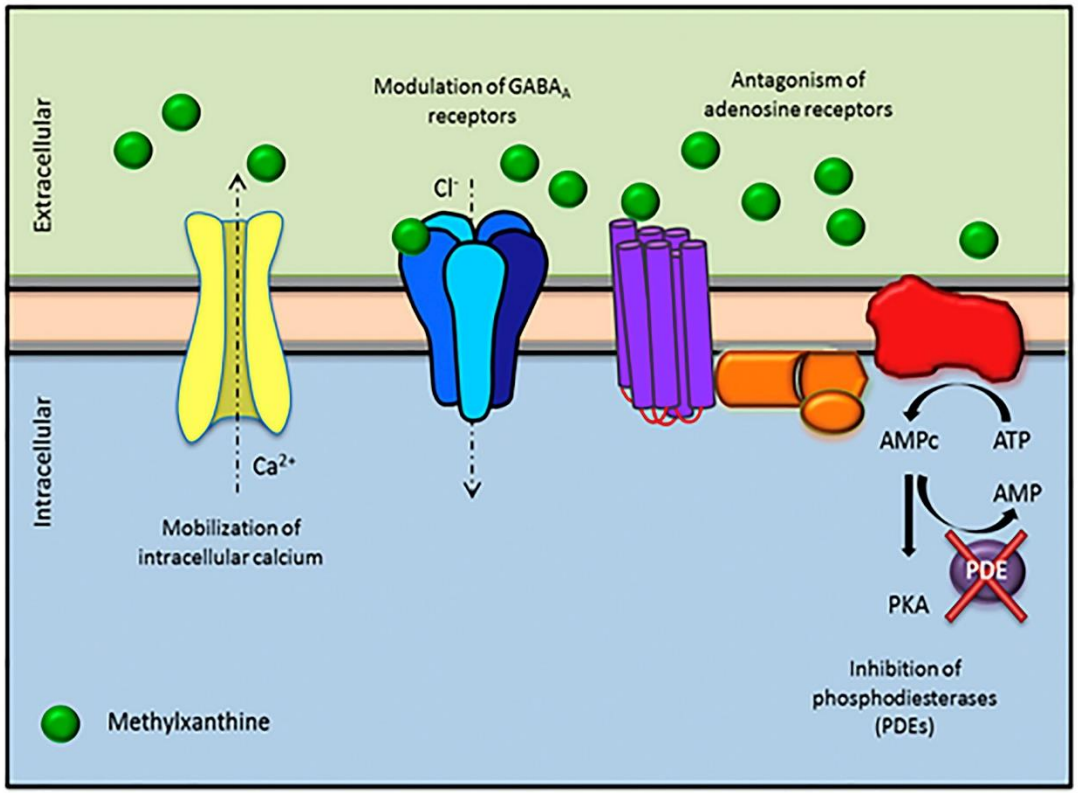
  - Methylxanthines inhibits cyclic nucleotide phosphodiesterase (PDEs), thereby preventing conversion of cAMP and cGMP to 5'-AMP and 5'-GMP, respectively. Inhibition of PDEs will lead to an accumulation of intracellular cAMP and cGMP. Bronchodilataion, cardiac stimulation and vasodilatation occur when cAMP level rises in the concerned cells. Theophylline and related methylxanthines are relatively nonselective in the PDE subtypes inhibitor.
  - Theophylline is a competitive antagonist at adenosine receptors. Adenosine can cause bronchoconstriction in asthmatics and potentiate immunologically induced mediator release from human lung mast cells. Methylxanthines inhibits the adenosine action thereby casing bronchodilataion.

Theophylline





Central control of respiratory function



- Bronchodilatation
- Decrease pulmonary arterial pressure
- Increase the airway diameter

Asthma Drugs

Drugs

- Bronchodilators
- **Anti-secretory**
- Anti-leukotrienes
- Anti-inflammatory

Anti-secretory drugs

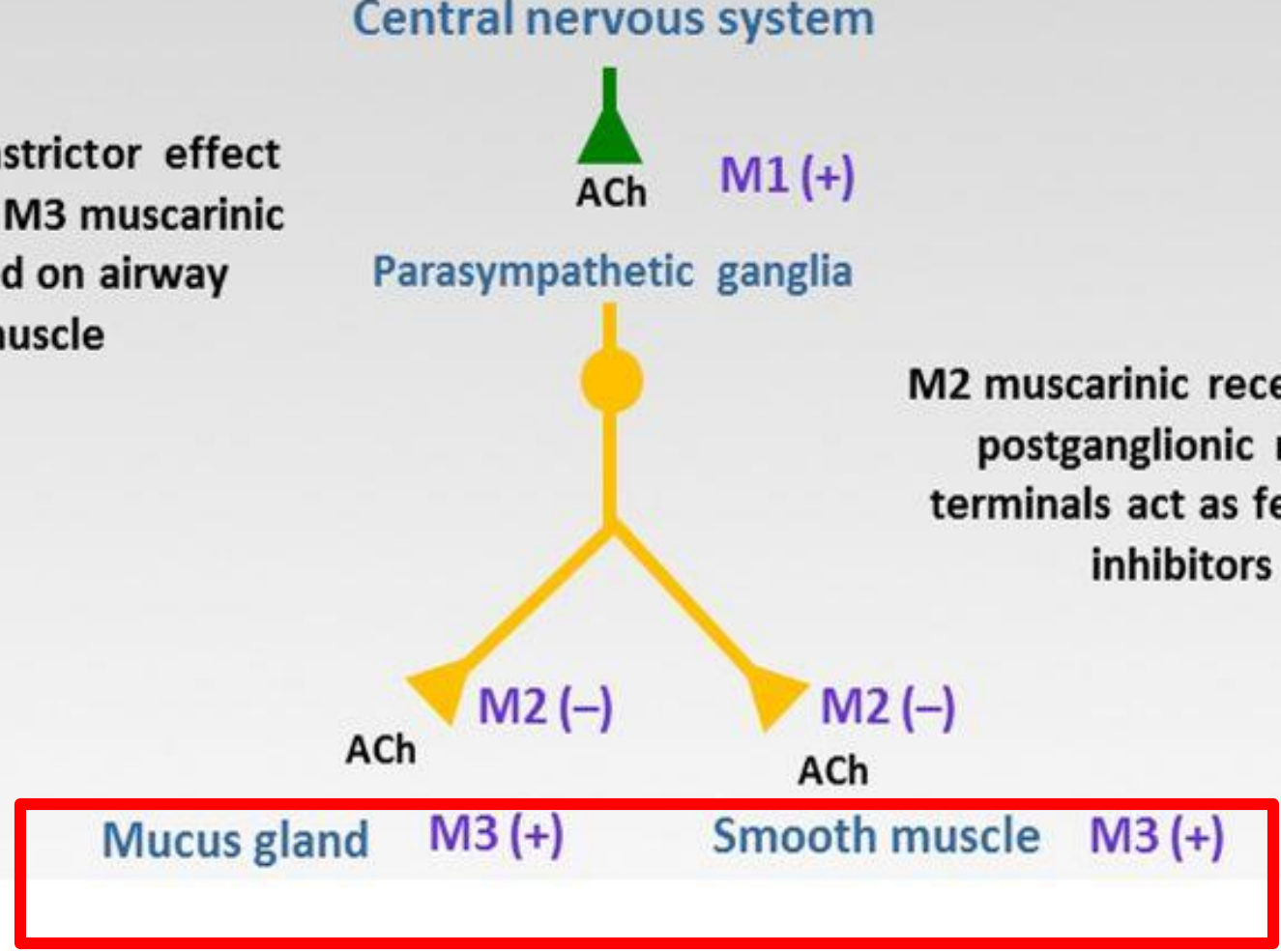
- Muscarinic receptor antagonists (e.g. ipratropium bromide) are second-line drugs

  —inhibits acetylcholine-mediated bronchospasm
  —binds to all muscarinic receptor subtypes (M_1, M_2 and M_3)
  —is given by aerosol inhalation.

Muscarinic Antagonists (M1-**M3**)

- Ipratropium
- Oxitropium
- Tiotropium bromide

Inhibit bronchoconstrictor effect of acetylcholine at M3 muscarinic receptors located on airway smooth muscle



M2 muscarinic receptors on postganglionic nerve terminals act as feedback inhibitors

Roux et al. Gen Pharmac

Asthma Drugs

Drugs

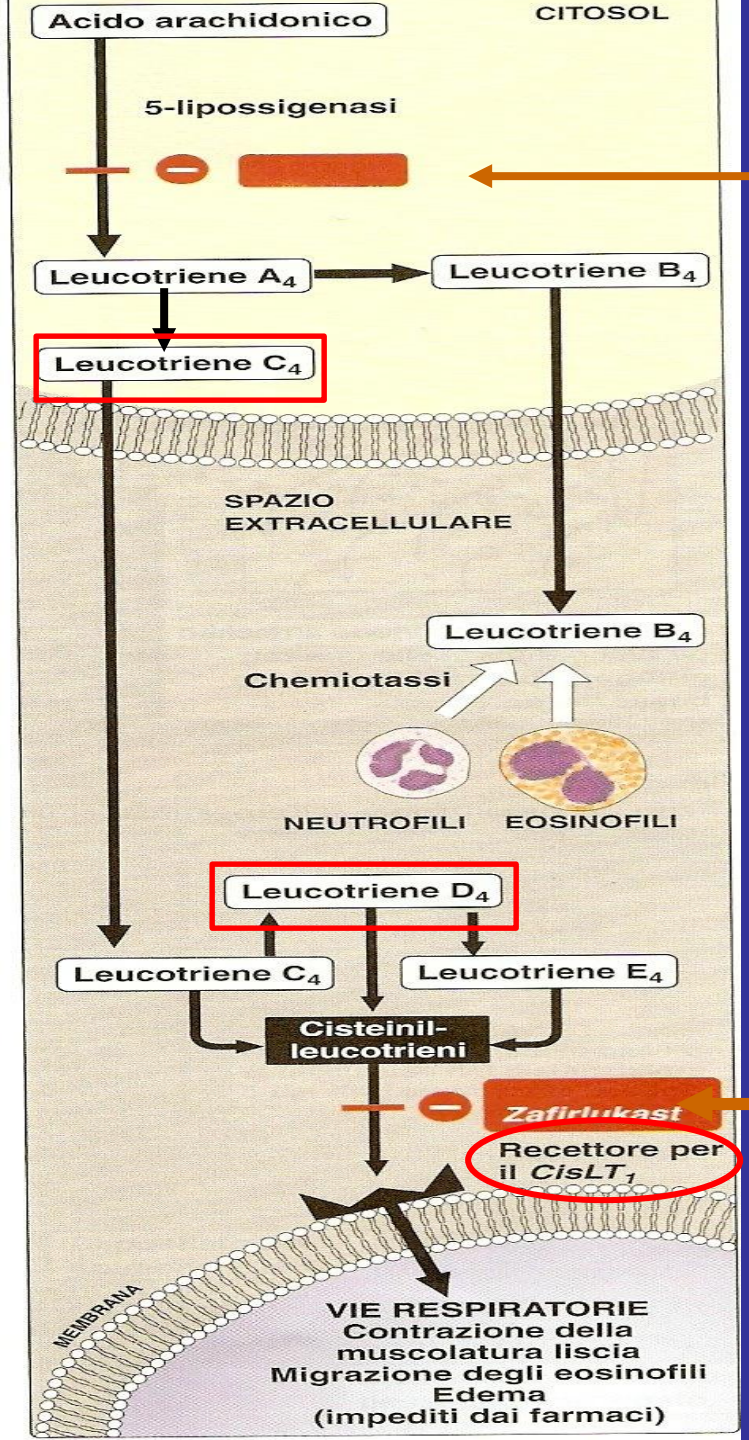
- Bronchodilators
- Anti-secretory
- **Anti-leukotrienes**
- Anti-inflammatory

Modifying agents of leukotrienes

Bronchial asthma drugs

Leucotrienes C4 and D4

- Cysteinyl-leukotriene receptor antagonists (e.g. montelukast):
  - —competitively inhibit cysteinyl leukotriene receptors
  - —inhibit exercise-induced bronchospasm and aspirin-induced asthma
  - —have a bronchodilator action that is additive with β_2-adrenoceptor agonists
  - —are of use mainly as add-on therapy for mild-to-moderate asthma



Zileuton

Action sites of leukotriene modifying drugs

Zafirlukast
Montelukast
Pranlukast

In combination with Beta2 agonists

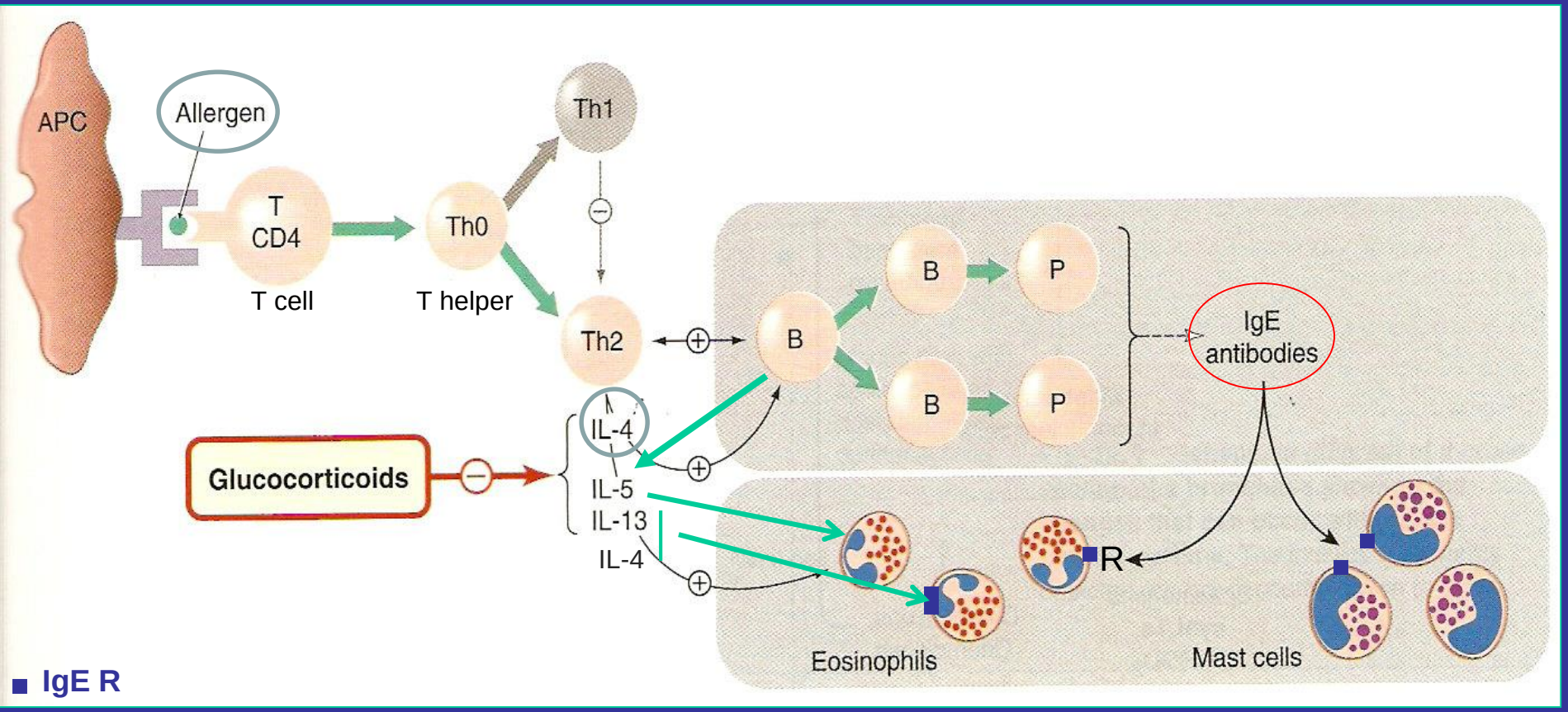
Asthma Drugs

Drugs

- Bronchodilators
- Anti-secretory
- Anti-leukotrienes
- **Anti-inflammatory**

Anti-inflammatory drugs
Glucocorticoids

Role of T lymphocytes in asthma



APC = antigen presenting cell
P = plasma cell
IgE = Immunoglobulins

Clinical use of glucocorticoids in asthma

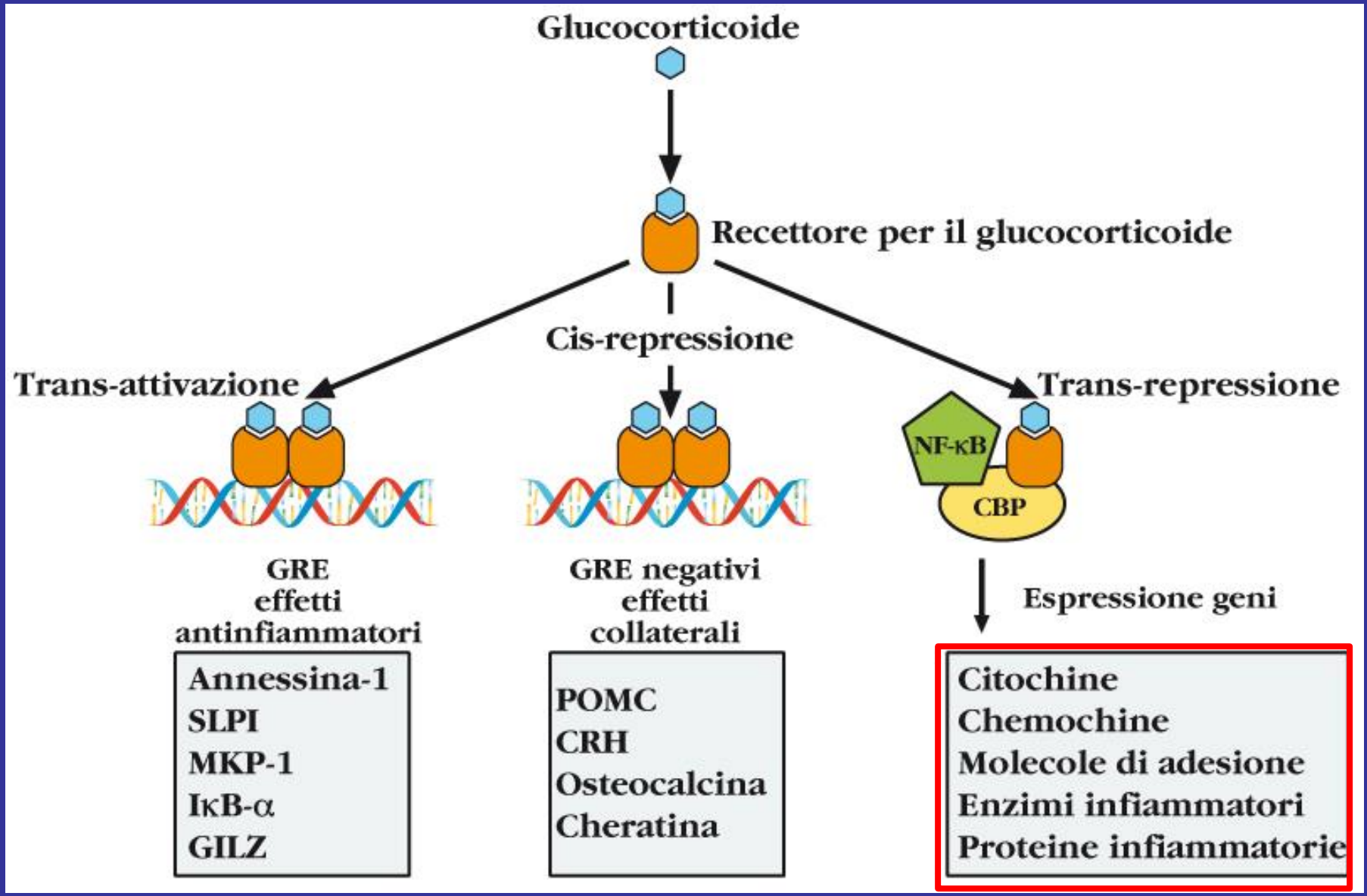
- Patients who require regular bronchodilators should be considered for glucocorticoid treatment (e.g. with inhaled beclometasone).
- More severely affected patients are treated with high-potency inhaled drugs (e.g. budesonide) and additional agents (e.g. slow release theophylline).
- Patients with acute exacerbations of asthma may require intravenous hydocortisone and oral prednisolone.
- A 'rescue course' of oral prednisolone may be needed at any stage of severity if the clinical condition is deteriorating.
- Prolonged treatment with oral prednisolone, in addition to inhaled bronchodilators and steroids, is needed by a few severe asthmatics.

Antiasthma drugs: anti-inflammatory agents

Glucocorticoids

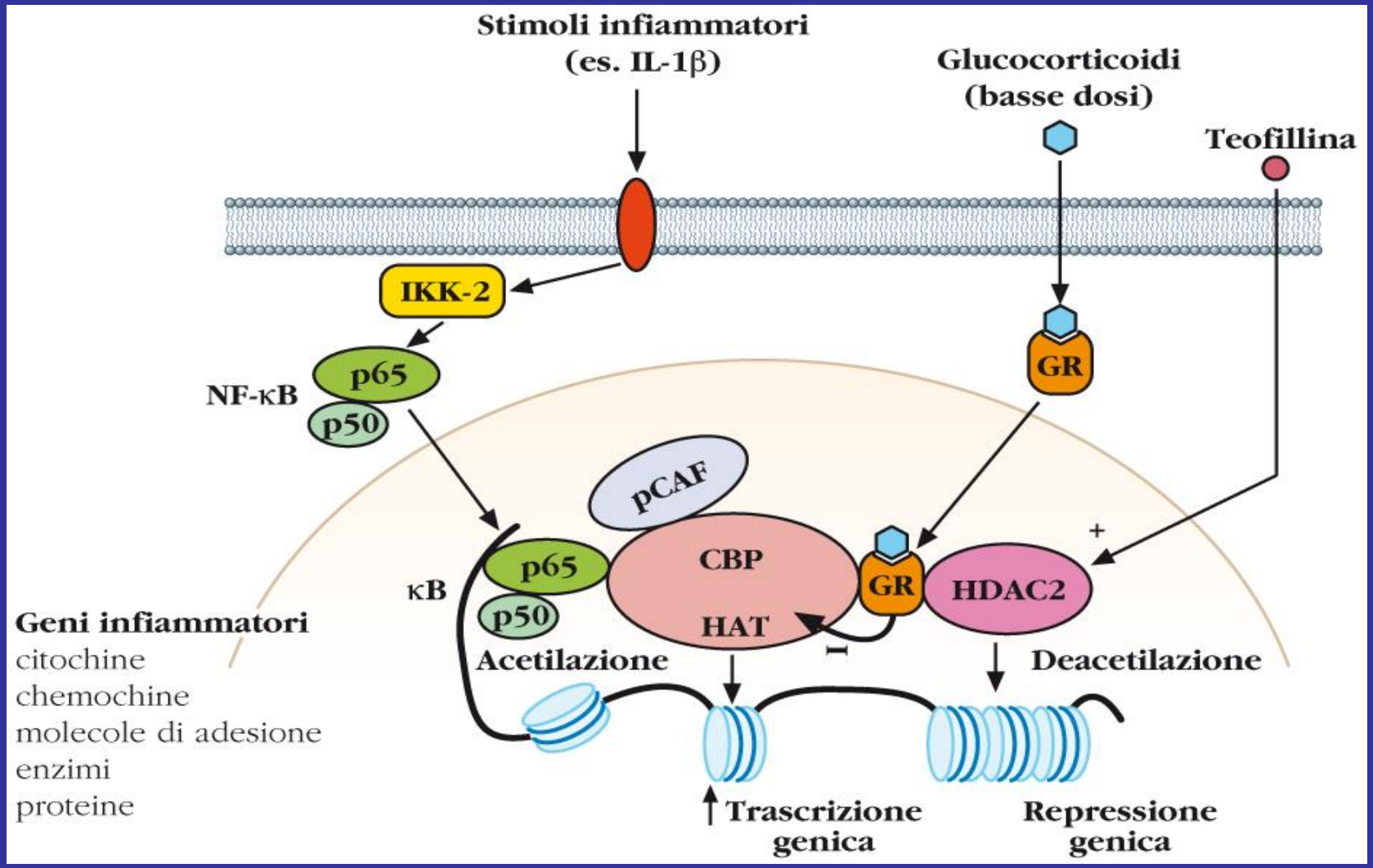
- These reduce the inflammatory component in chronic asthma and are life-saving in status asthmaticus (acute severe asthma).
- They do not prevent the immediate response to allergen or other challenges.
- The mechanism of action involves decreased formation of cytokines, particularly those generated by Th2 lymphocytes decreased activation of eosinophils and other inflammatory cells.
- They are given by inhalation (e.g. **beclometasone**); systemic unwanted effects are uncommon at moderate doses, but oral thrush and voice problems can occur. Systemic effects can occur with high doses but are less likely with **mometasone** because of its presystemic metabolism. In deteriorating asthma, an oral glucocorticoid (e.g. **prednisolone**) or intravenous **hydrocortisone** is also given.

Effects of glucocorticoids on gene expression



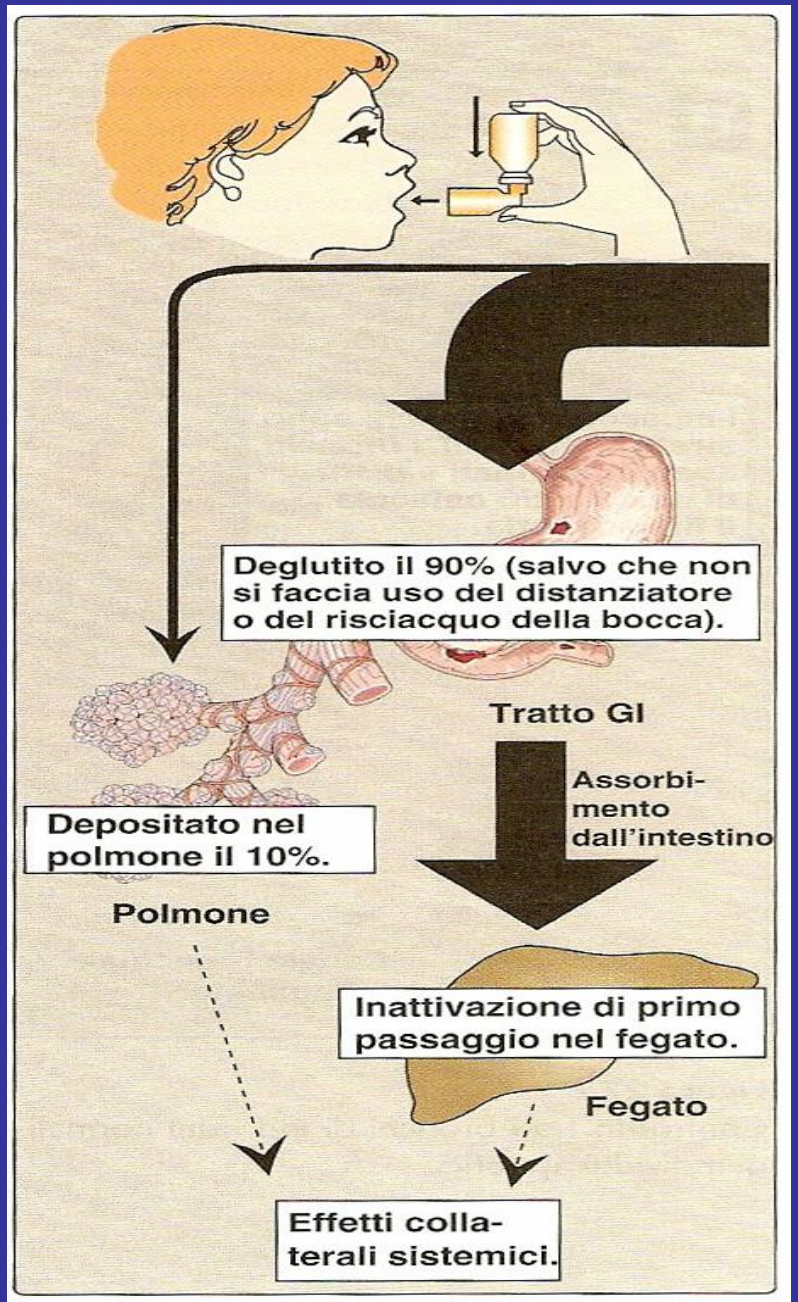
GRE- glucocorticoid response element; SLPI- Secretory leucoprotease Inhibitor; MKP1- Mitogen-activated protein kinase phosphatase 1; CBP- CREB binding protein; IkB- inhibitor NF-kB; GILZ- Gluc induced-leucine zipper

Mechanism of inhibition of expression of inflammatory genes (deacetylation) by glucocorticoids and theophylline

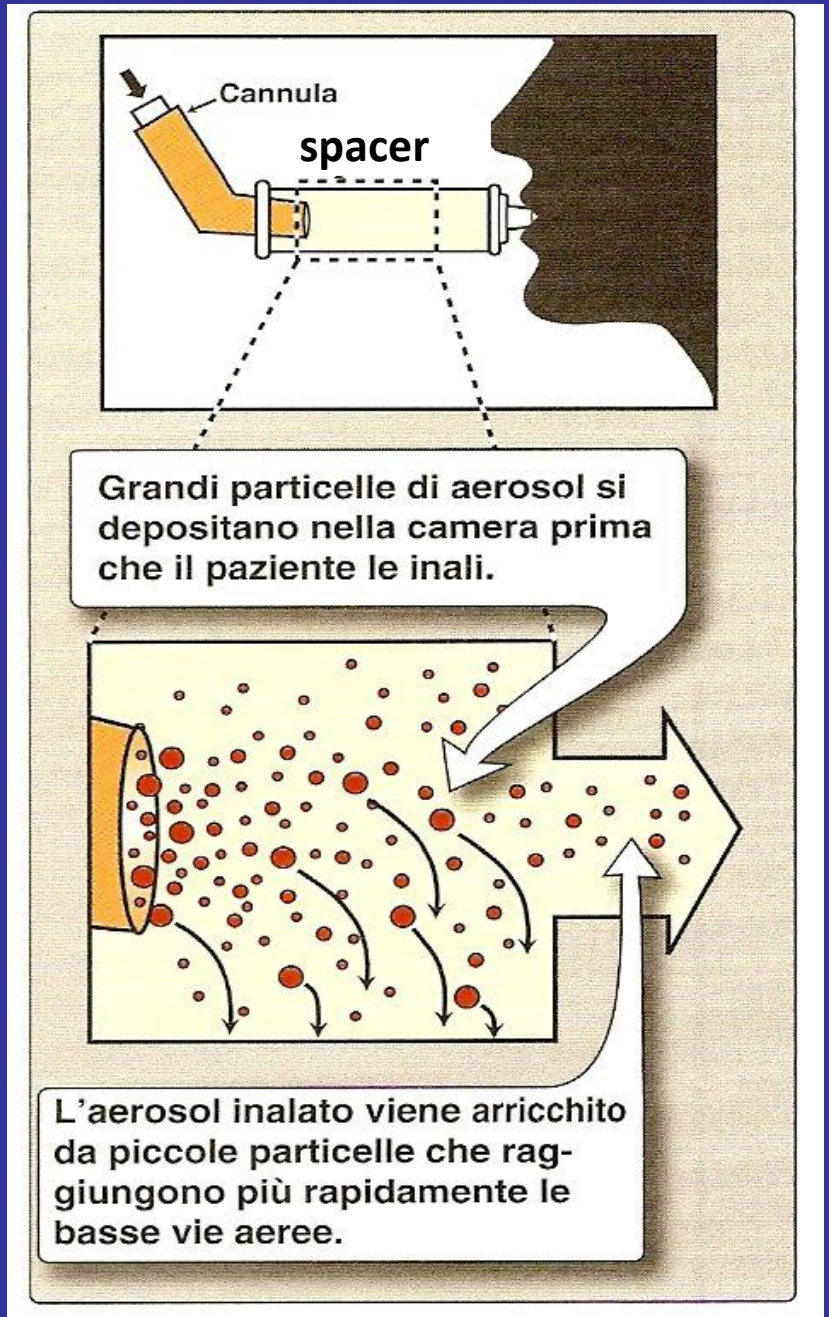


pCAF - activating factor; HAT- histone acetylation; **HDAC2 = histone deacetylase 2**

Pharmacokinetics of inhalatory glucocorticoids



Effect of the spacer on the delivery of an inhalable aerosol



Classification of asthma severity and treatment

(Beta2 agonists)

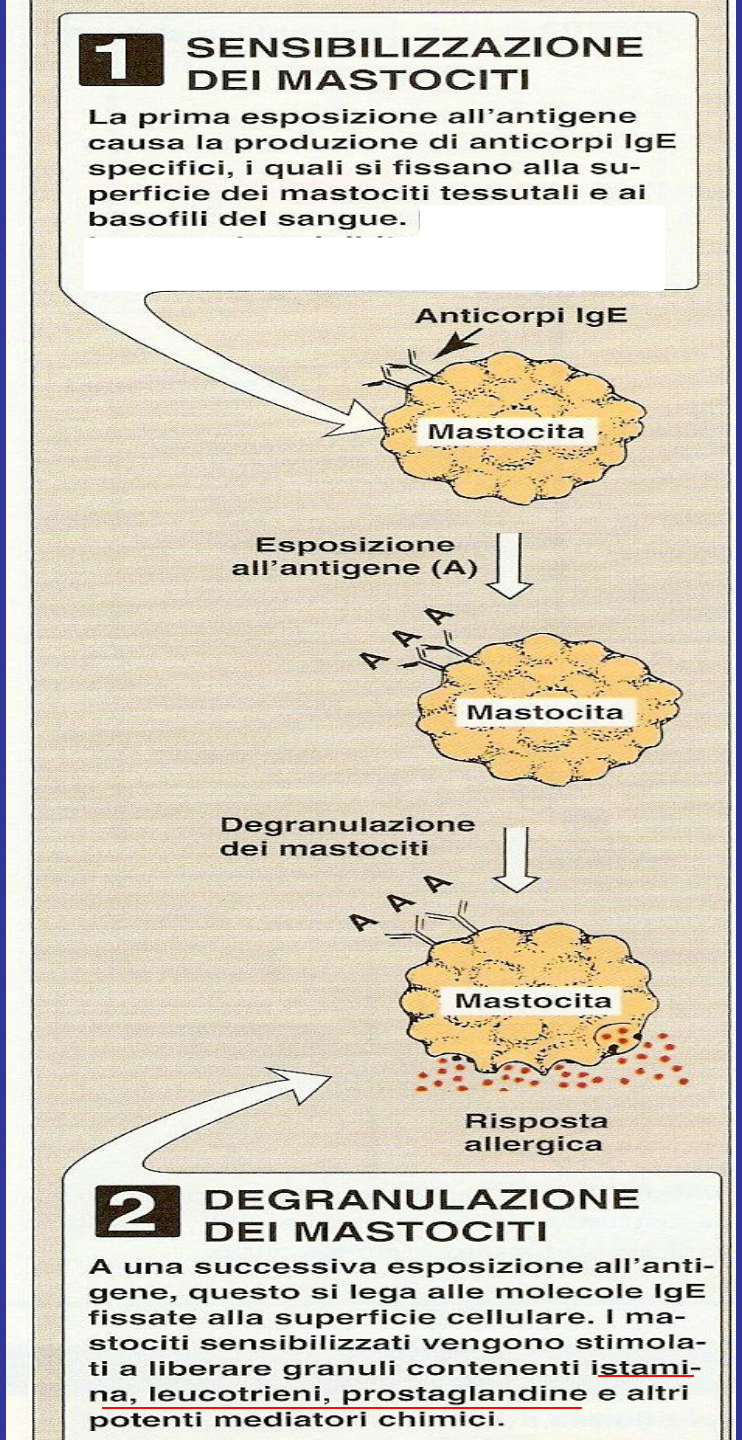
CLASSIFICAZIONE	EPISODI BRONCO-COSTRITTIVI	RISULTATI DEL FLUSSO DI PICCO O DELLA SPIROMETRIA	CONTROLLO A LUNGO TERMINE	SOLLIEVO RAPIDO DEI SINTOMI
Lieve intermittente	Meno di due per settimana	Quasi normale*	Nessuna terapia quotidiana	β_2-agonisti a breve durata *
Lieve persistente	Più di due per settimana	Quasi normale*	Corticosteroidi inalatori a bassa dose	β_2-agonisti a breve durata *
Moderata persistente	Quotidiani	Dal 60 all'80% del normale	Corticosteroidi inalatori a dose medio-bassa e un β_2-agonista a lunga durata §	β_2-agonisti a breve durata *
Severa persistente	Continui	Meno del 60% del normale	Corticosteroidi inalatori ad alta dose e un β_2-agonista a lunga durata §	β_2-agonisti a breve durata *

* Salbutamol, pirbuterol, terbutaline (15-30 min up to 4-6 h)

§ Salmeterol, formoterol (up to 12 h)

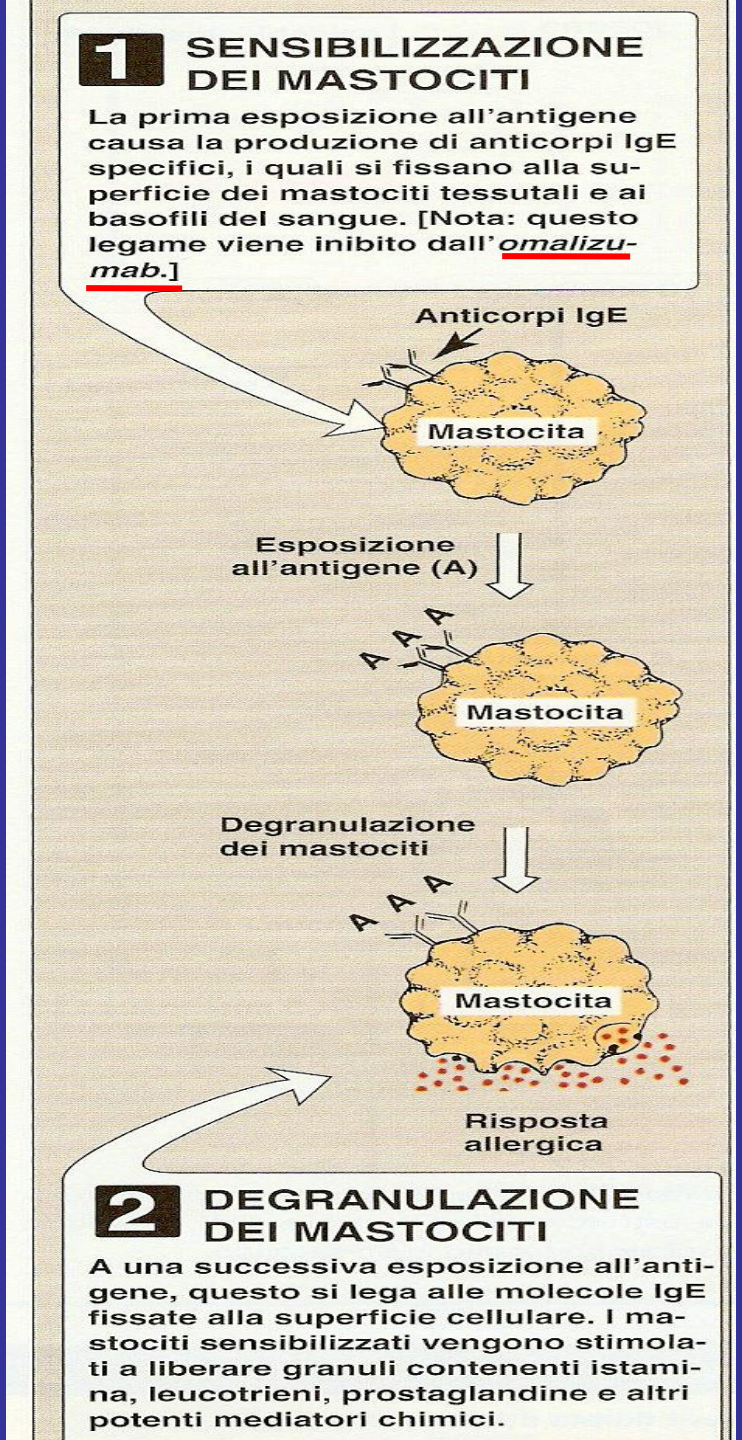
Prophylaxis
Cromoglycate and nedocromil

Hypersensitivity reactions mediated by immunoglobulins



- Inhibits macrophages, eosinophils, neutrophils, monocytes
- Reduces hyperpolarization in inflamed cells which activates increased Ca++ responsible for degranulation

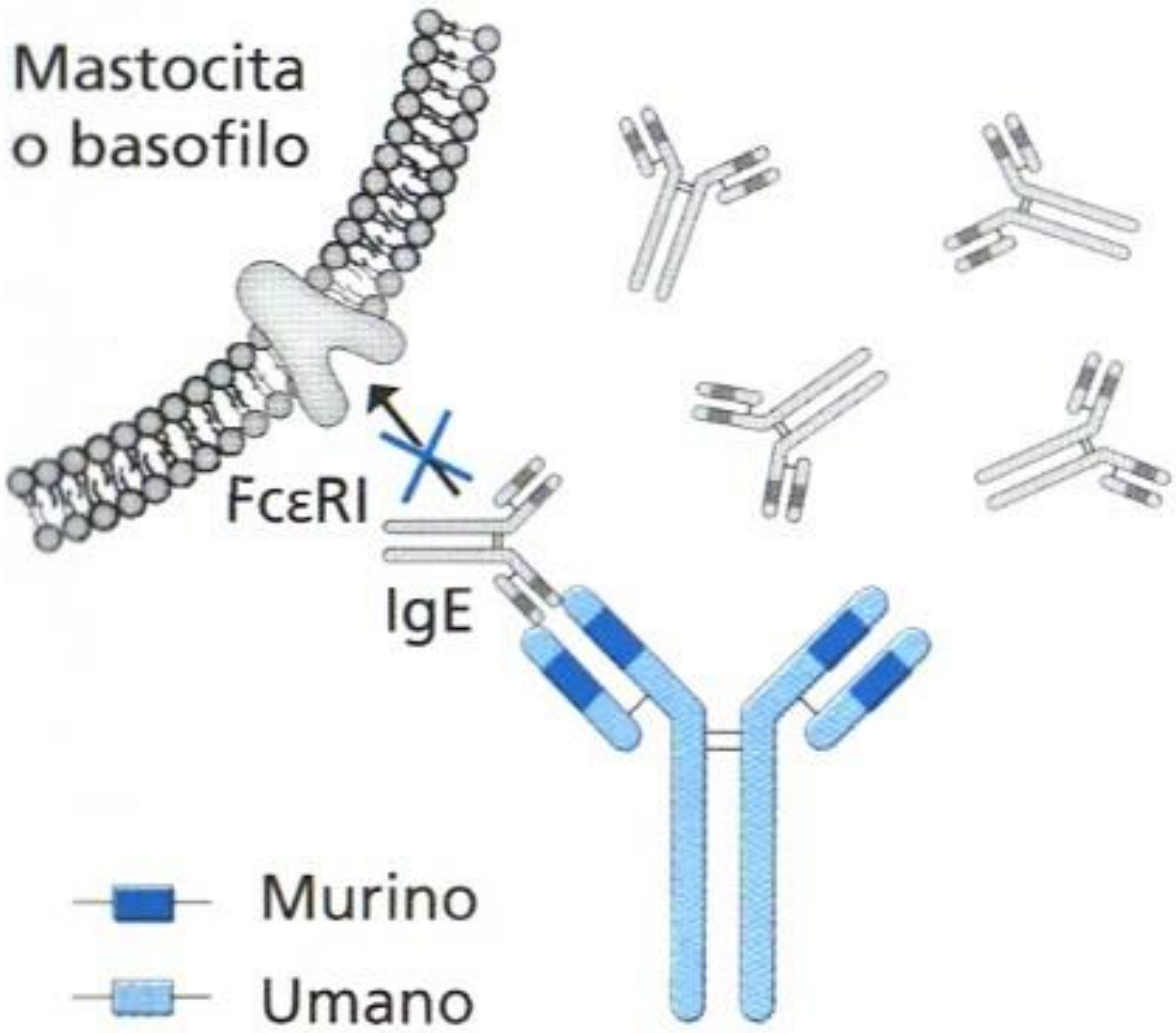
Anti-IgE treatment



Hypersensitivity reactions mediated by immunoglobulins

Omalizumab

In severe allergic asthma



AB omalizumab binds IgE receptor

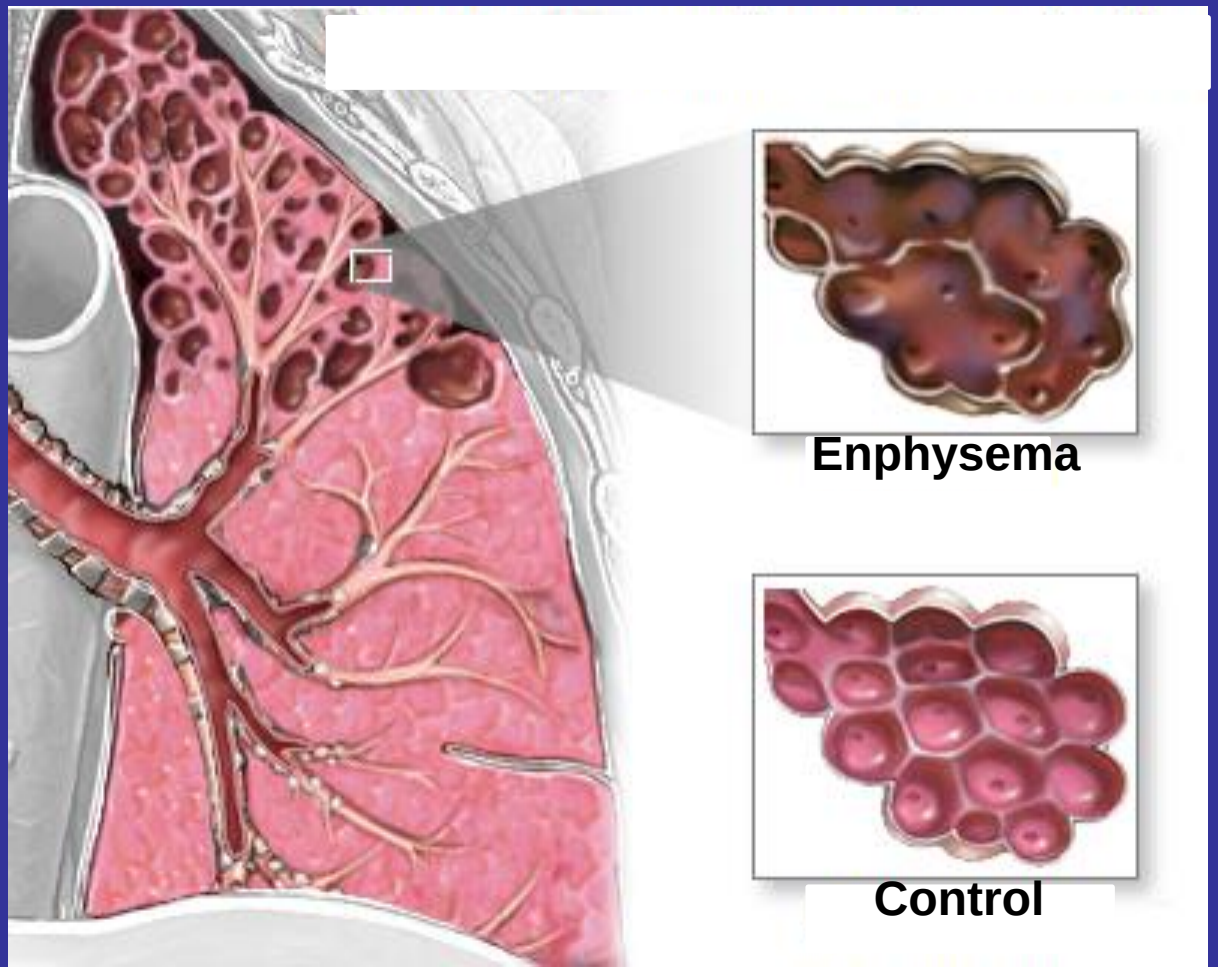
Therapeutic Strategies

- Long-Acting Beta-adrenergic Agonist (LABA) + glucocorticoid (GC) anti-inflammatory by inhalation

- LABA + GC via inhalation + slow-release theophylline or leukotriene inhibitors or tiotropium bromide

- Addition of oral treatment with GC

Chronic obstructive pulmonary disease (COPD)



Treatment of stable chronic obstructive pulmonary disease (COPD)

STADIO	CARATTERISTICHE	CONTROLLO A LUNGO TERMINE
I: BPCO lieve	FEV_1 superiore all'80% del previsto	Broncodilatatori a breve durata d'azione al bisogno.
II: BPCO moderata	FEV_1 dal 50 all'80% del previsto	Trattamento costante con uno o più broncodilatatori. Glucocorticoidi inalatori.
III: BPCO severa	FEV_1 meno del 30% del previsto	Trattamento costante con uno o più broncodilatatori. Glucocorticoidi inalatori. Antibiotici per le esacerbazioni acute della BPCO caratterizzate da aumento del volume e della purulenza delle secrezioni. Ossigenoterapia a lungo termine.

FEV = forced expiratory volume 1sec

Drugs for chronic asthma therapy: pharmacokinetic aspects

Farmaci	Via di somministrazione	Biodisponibilità	Vd	Emivita	Legame alle proteine plasmatiche	Frequenza di somministrazione	Metabolismo	Eliminazione
Glucocorticoidi							–	–
beclometasone	inalatoria	–	–	–	–	6 – 12 h	–	–
budesonide	inalatoria	–	–	–	–	12-24 h	–	–
flunisolide	inalatoria	–	–	–	–	12-24 h	–	–
fluticasone	inalatoria	–	–	–	–	12 h	–	–
triamcinolone	inalatoria	–	–	–	–	6-12 h	–	–
Antagonisti dei leucotrieni								
montelukast	per os	58-66%	8 -11 L	2,7-5,5 h	> 99%	ogni 24 h	epatico: CYP 3A4 e 2C9	prevalentemente biliare (farmaco e metaboliti)
zafirlukast	per os	sconosciuta	70 L	8-16 h	> 99%	ogni 12 h	epatico: CYP2C9	prevalentemente biliare (farmaco e metaboliti)
Cromoni	inalatoria	-		-	-	ogni 6 h		
Teofillina**	per os	90-100%	35 L	8 h***	60%****	ogni 12 h	epatico: demetilazione, ossidazione	renale

Anti-asthmatic drugs: side effects and dosage

Farmaco	Posologia	Effetti collaterali
Glucocorticoidi inalatori		locali: raucedine, candidosi oro-faringea; sistemici: riduzione cortisolemia*, osteoporosi, cataratta (rara), atrofia cutanea**, porpora**, possibile ritardo dell'accrescimento
beclometasone	100 – 2000 µg	
budesonide	100 – 1600 µg	
flunisolide	500 - > 2000 µg	
fluticasone	100 – 2000 µg	
triamcinolone	400- > 2000 µg	
β_2-Adrenergici a lunga durata di azione		tremore, possibile aumento della iperreattività bronchiale se non associati a glucocorticoidi inalatori; iperglicemia, ipopotassiemia, aumento delle concentrazioni plasmatiche di acido lattico. A dosi superiori a quelle terapeutiche: tachicardia, palpitazioni.
formorterolo	9-24 µg	
salmeterolo	50-100 µg	
Antagonisti dei leucotrieni		
montelukast	10 mg (nell'adulto); 5 mg (nel bambino età 6-14 anni)	cefalea, dispepsia, dolore addominale; associazione con sindrome di Churg-Strauss
zafirlukast	40 mg	cefalea, dispepsia, dolore addominale, aumento delle concentrazioni plasmatiche di transaminasi; associazione con sindrome di Churg-Strauss
Cromoni		
nedocromil sodico	8 mg	molto raramente broncocostrizione, edema laringeo, artralgie, angioedema, cefalea, eruzioni, cutanee
Teofillina	0,4-0,5 mg/kg/h	anoressia, nausea, emesi, insonnia, agitazione, palpitazioni, ipotensione; ad alte concentrazioni plasmatiche***, aritmie e convulsioni