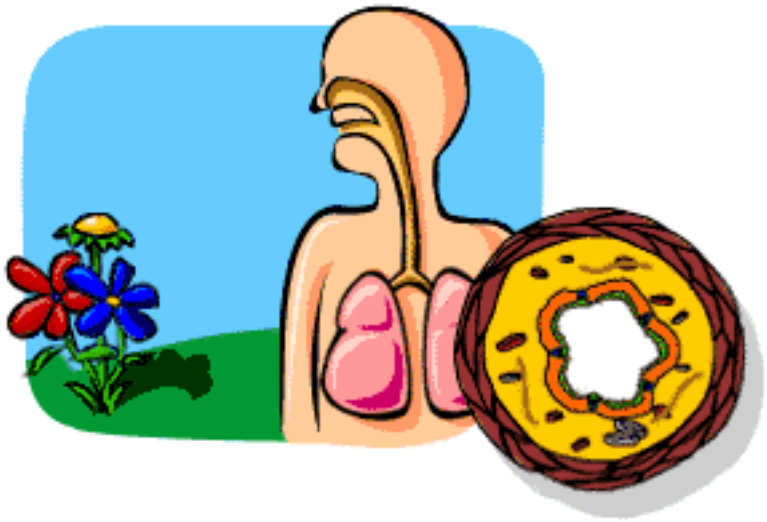
PHARMACOLOGY OF RESPIRATORY SYSTEM

Ladislav Mirossay

P. J. Šafárik University
Faculty of Medicine
Department of Pharmacology
Košice



BRONCHIAL ASTHMA

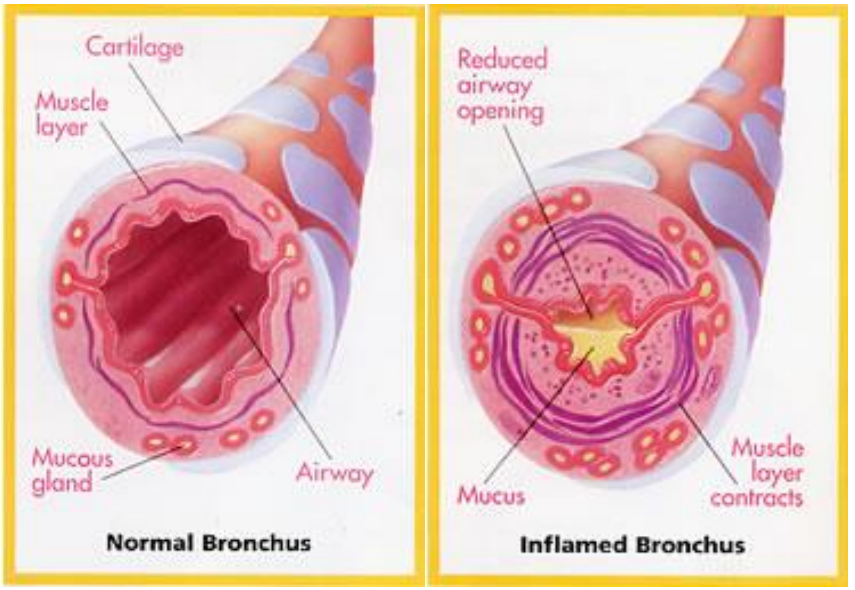
- Syndrom of recurrent reversible obstruction of airways in response to stimulus

- Patient suffers from intermittent attacks of:

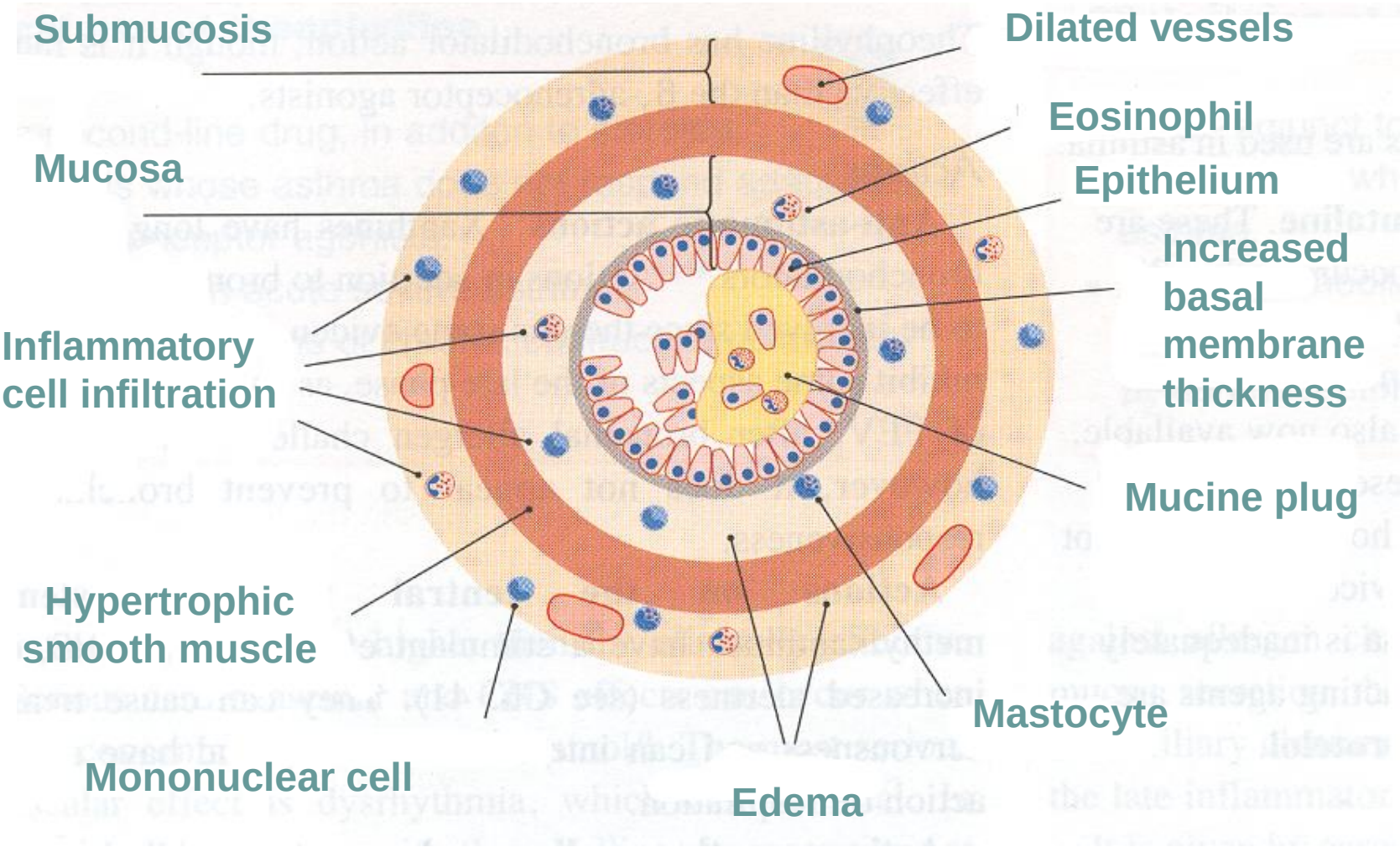
  - **dyspnoe, wheezing, cough**
  - **respiratory failure**
  - **expiration dyspnoe**

Patologic & anatomic background

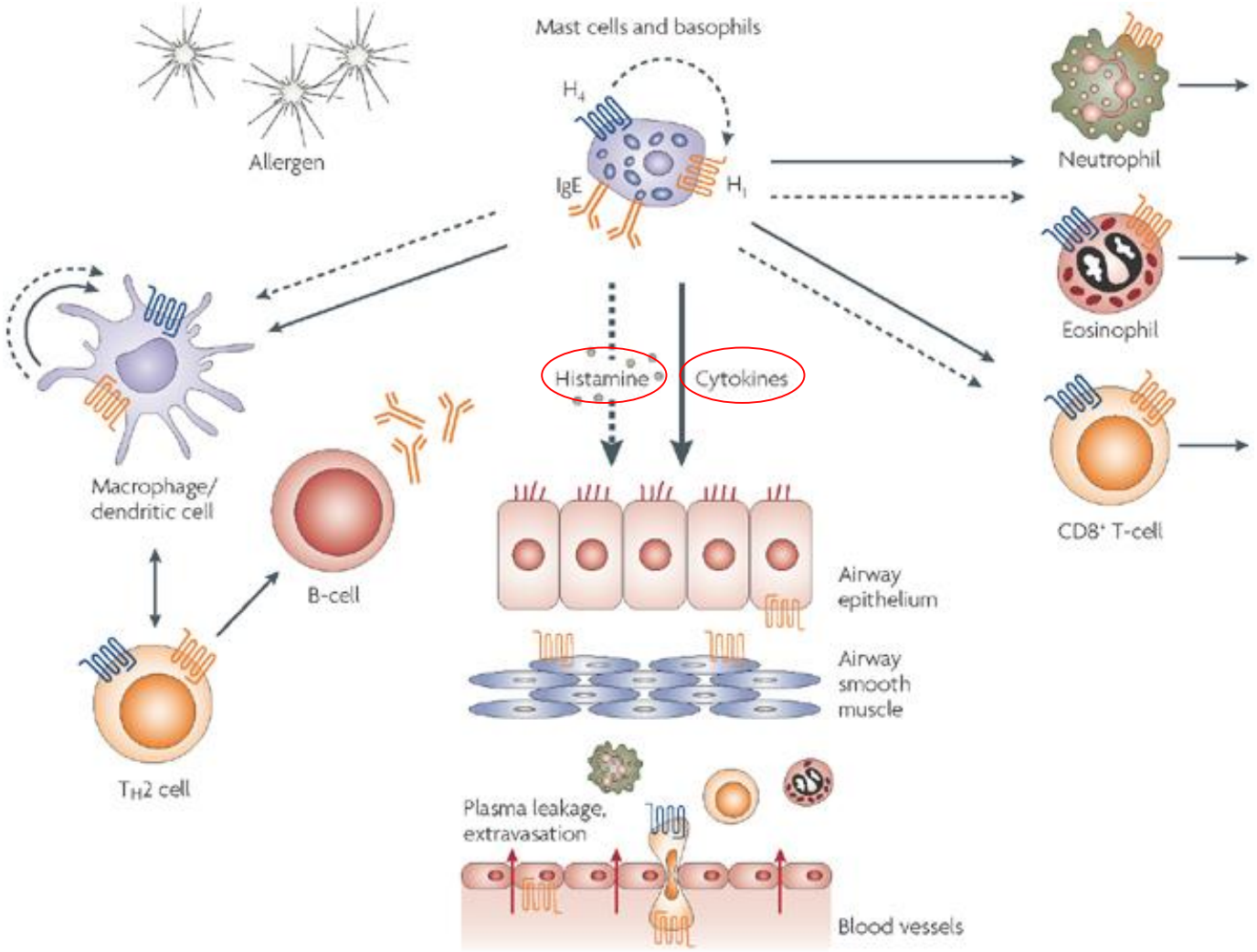
- Contraction of respiratory smooth muscles
- Mucosal edema
- Viscous mucin secretion in bronchial lumen



Participants of bronchial obstruction



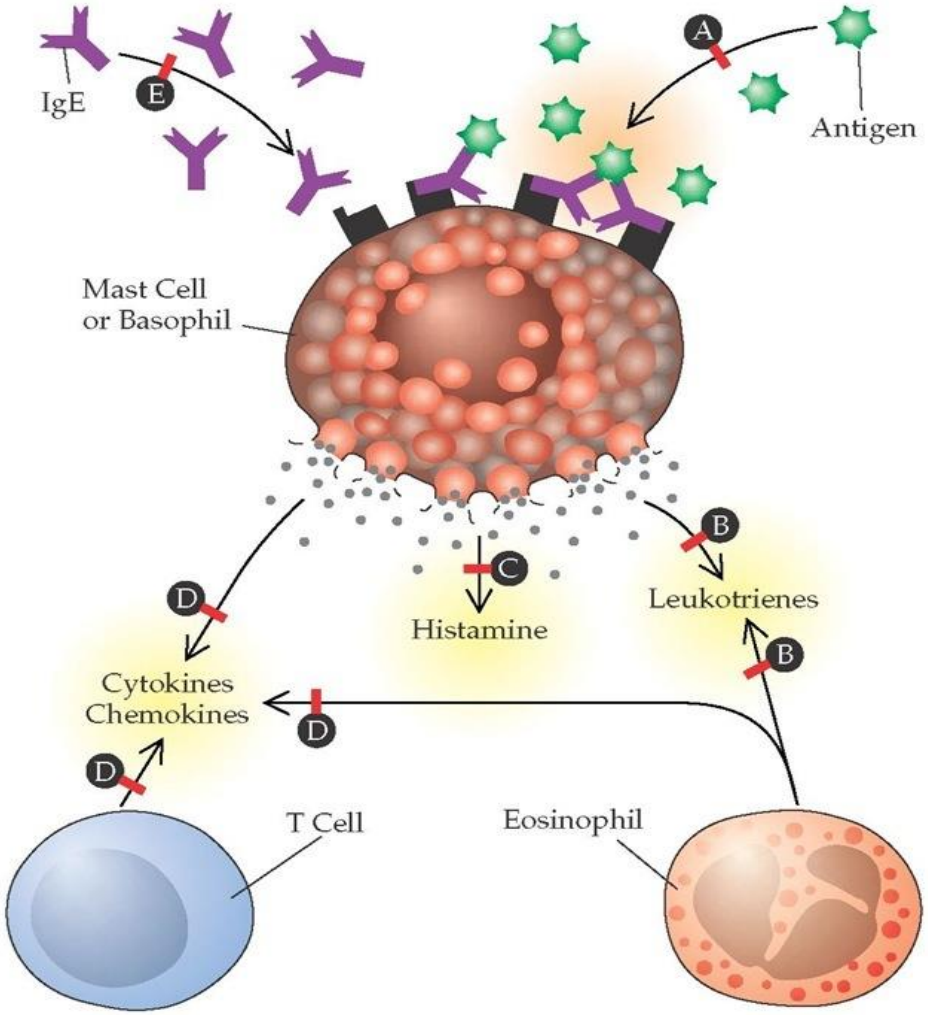
Cellular events after active factors release



Nature Reviews | Drug Discovery

Asthma bronchiale

Particular step influence



A. Environmental control
B. Leukotriene antagonists
C. Antihistamines
D. Corticosteroids
E. Anti-IgE therapy
(omalizumab)

Pharmacologic intervention

- Edema & cell infiltration:

ANTIINFLAMMATORY DRUGS

- Smooth muscle contraction & bronchial obstruction:

BRONCHODILATING DRUGS

Ways of application

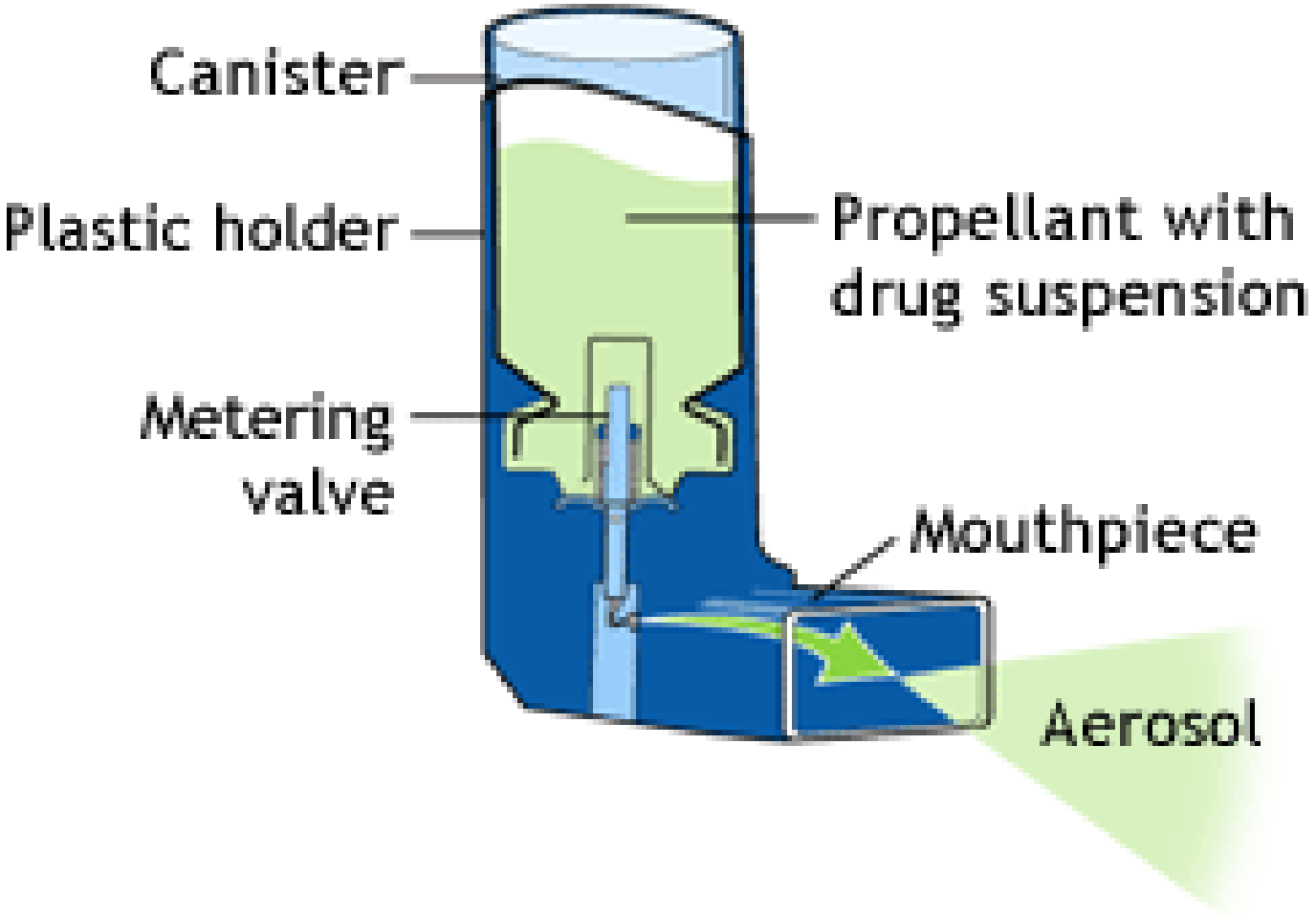
- **Inhalatory**
  - **aerosol**
  - **dry powder**

- **Oral**

- **Inj.**

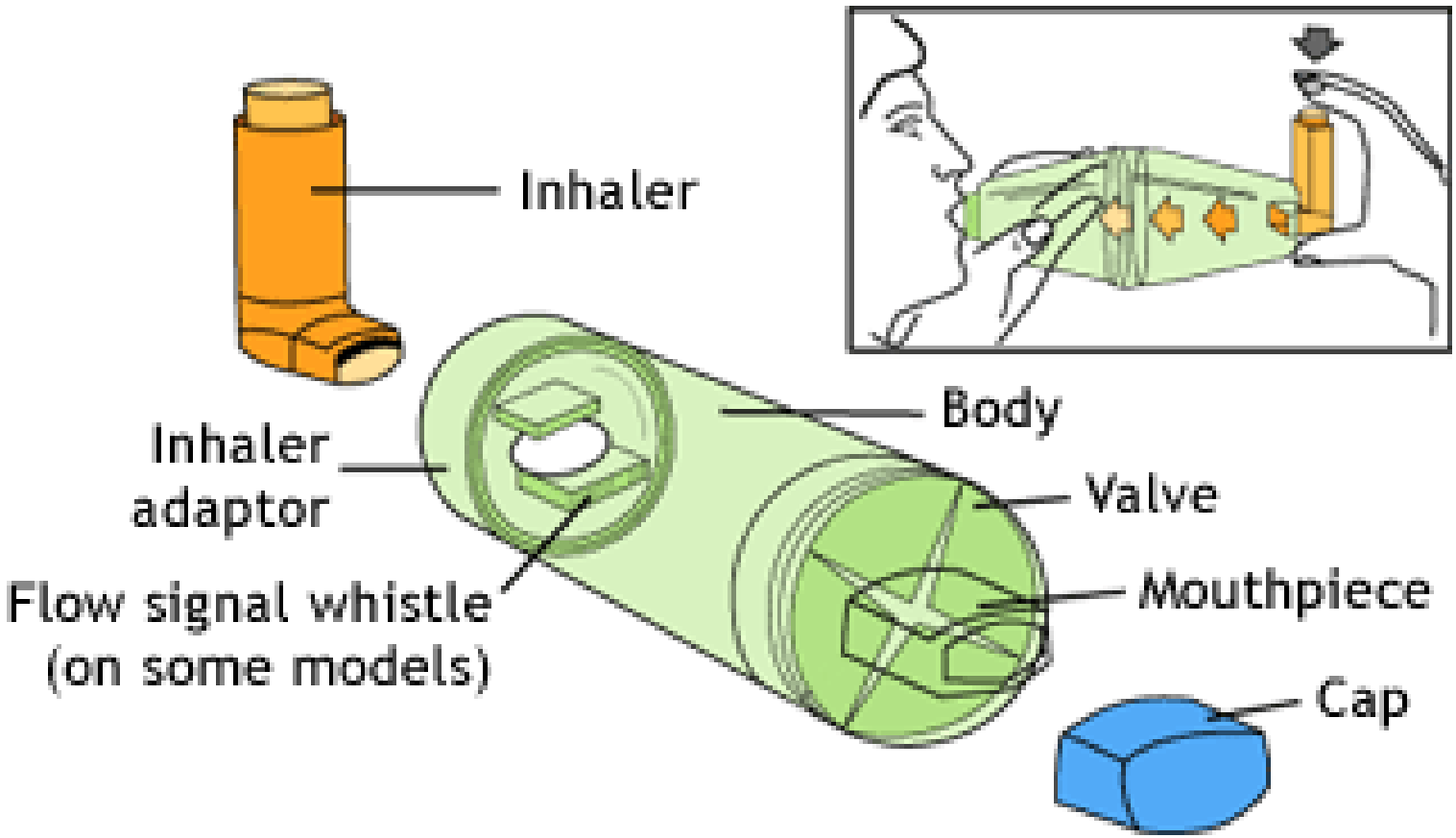
Inhalatory application

Adults

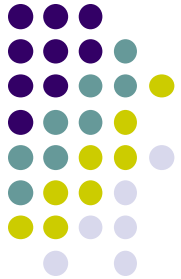


Inhalatory application

Spacer - children



ANTIINFLAMMATORY DRUGS



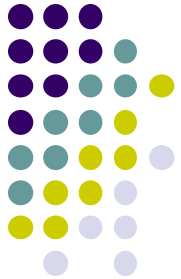
- ***CORTICOSTEROIDS***

⇓ or modify inflammatory response of bronchi

- ***INHIBITORS OF MASTOCYTE DEGRANULATION***

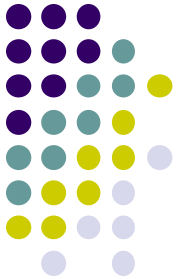
⇓ inflammatory & allergy mediator release

Inhaled corticosteroids
ICS



- The most effetive method of SE diminution/elimination
- The most effetive long therm preventive therapy
- Early diagnosis & therapy prevents remodelation of airways
- Daily doses are minimal (in μg)

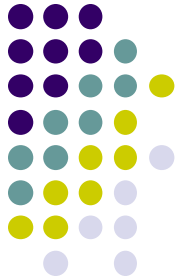
Selected drugs



- ***Beclomethasone, budesonide & fluticasone***
  with minimal systemic absorption & SE:
  - mean daily doses: 100 - 2000 µg

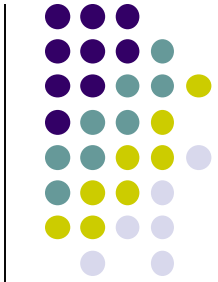
- **Minimal SE:**
  - oropharyngeal candidoses
  - voice disturbance

Chronic use of ICS



- Effectively ⇓ symptoms & ⇑ lung functions
- ⇓ bronchial hyperreactivity
- Maximal effect is attained after 9 to 12 month therapy
- Do not affect growth of children

The role of ICS in stable asthma



- The controller medication of choice for management of stable asthma
- All the ICS are equally efficacious when used in equipotent doses
- Most of the clinical benefit from ICS is obtained at low to moderate doses
- ICS should be started at low to moderate dose (depending on the severity of symptoms at presentation) & be used at lowest possible dose required
- High-dose ICS use should preferably be avoided to ⇓ the risk of SE (both local & systemic)

Oral corticosteroids
OCS

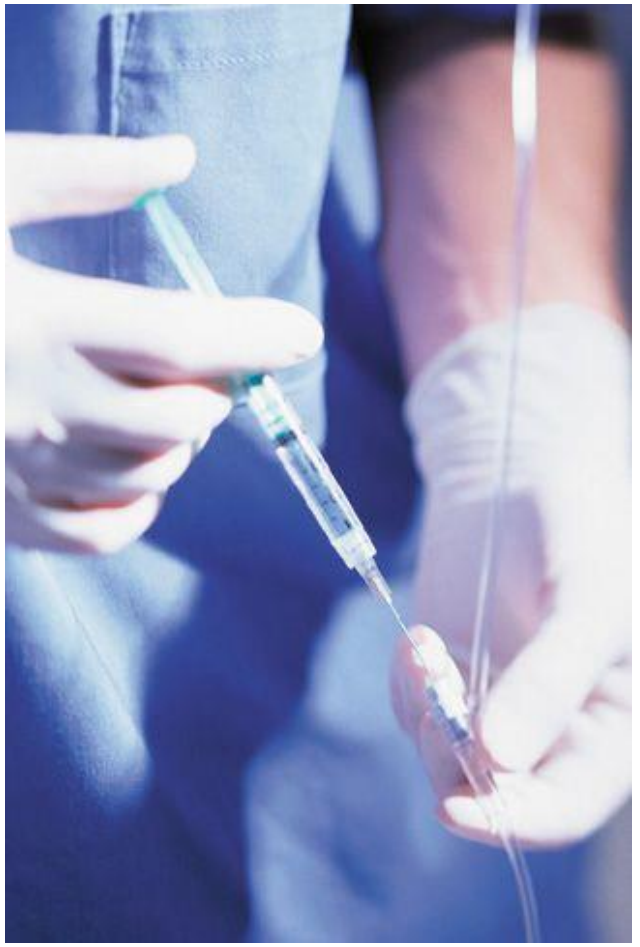
- Because of SE, reserved for patients with severe asthma & no adequate response after treatment with:

inhalatory steroids or bronchodilators

- ***Prednisone*** 30 - 60 mg/day orally:
  - in majority of patients can be terminated in one week

Corticosteroids - i.v.

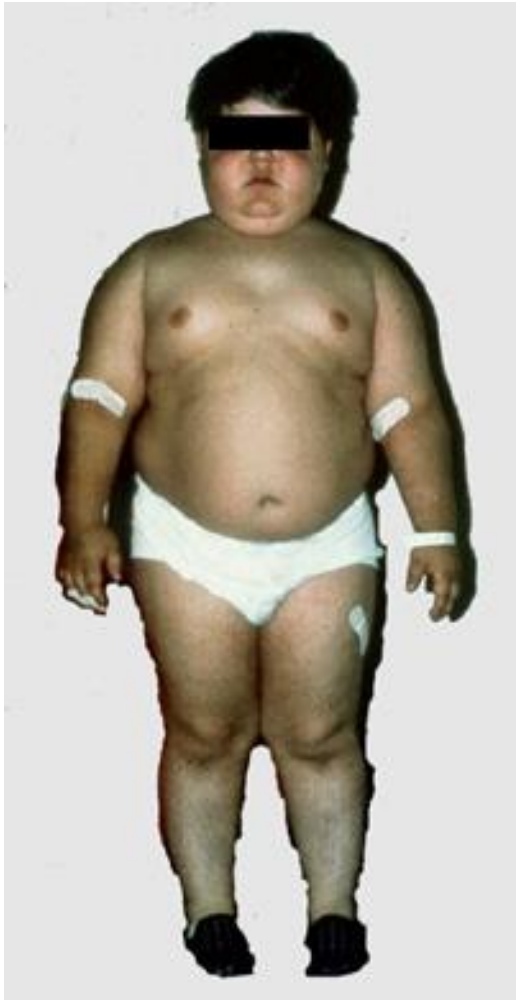
- **Severe cases**
- **Lifethreatening situations**
- ***Status asthmaticus***



Systemic SE
Oral & i.v. corticosteroids

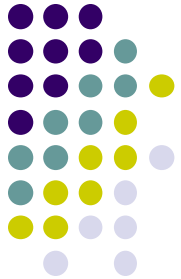
- Gluconeogenesis (hyperglycemia)
- Hypertension
- Immunosuppression
- Adrenal suppression
- Osteoporosis
- Growth retardation in children
- Cataract
- Glaucoma

- CUSHING SYNDROME



Mast cell degranulation inhibitors

MCDI



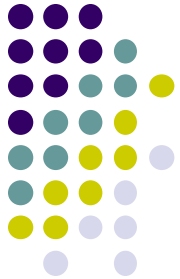
- Prevention of bronchoconstriction
- Effectively ⇓ mast & inflammatory cells
- Effective in children after 4 - 6 weeks of application

MCDI
Indications & SE

Cromoglycate sodium
& nedocromil sodium

- Besides asthma also in allergic rhinitis, conjuctivitis
- SE: cough, taste disturbance, headache

Leukotriene receptor antagonists
LTRA



- cysteinyl-leukotrien-receptor antagonists

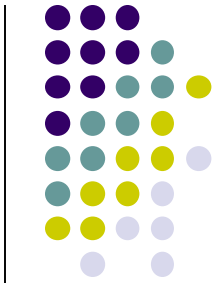
- *montelucast* - prevents antigen- & exertion-induced asthma
  - relaxes bronchi in moderate asthma
  - acts additively with β_2 - agonists

- 5-lipooxygenase inhibitors:

- *zileuton* - $\Downarrow$ LTC4, LTD4, LTB4 & leukocyte chemotaxine production in bronchial mucosa

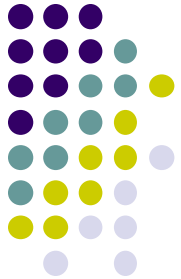
The role of LTRA & antimuscarinics

In stable asthma



- Monotherapy with LTRA is inferior to monotherapy with ICS
- Monotherapy with LTRA might be an alternative to ICS in patients with mild asthma (if they are unwilling to use ICS or if they are not suitable for ICS therapy)
- As add-on to ICS, LTRA are inferior to LABA
- Addition of LTRA might be beneficial in patients whose asthma remain uncontrolled (despite the ICS/LABA combination)
- ***Tiotropium*** may be used as add-on therapy if asthma remains uncontrolled (despite moderate-to-high-dose ICS & LABA combination therapy)

Bronchodilating drugs



- **SYMPATHOMIMETICS**

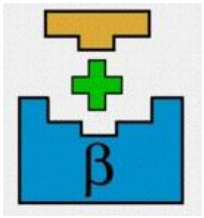
the most effective bronchodilators

- **METHYLXANTINES**

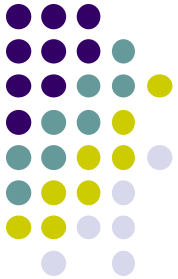
bronchodilators

- **ANTIMUSCARINIC AGENTS**

alternative bronchodilators



Sympathomimetics

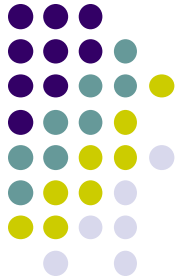


- **Non-selective:**
- *adrenaline* fast acting bronchodilator after s.c. application (1:1000)

  - maximal bronchodilation in 15 min after application, duration 60-90 min

- **SE:** tachycardia, arrhythmia, aggravation of angina pectoris

β_2-selective agonists



- **First choice bronchdilators:**
- *salbutamol, albuterol, terbutaline, fenoterol*

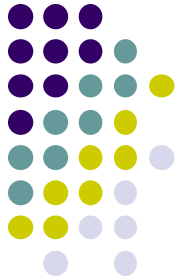
  in inhalatory form

  - effect in 5 min, maximal bronchodilation in 30-60 min, duration 2 h

  - even with particle size 2 - 5 μm 50 - 70% is traped in mouth & pharynx
- *terbutaline, fenoterol* exist also in oral tbl. form

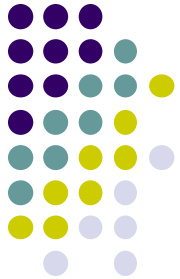
- **SE:**
- stenocardies
- tremor, insomnia, headache (in higher dose)

Long acting β_2-selective agonists
LABA



- **Longer duration** (12 h & more)
- *formoterol, salmeterol, clenbuterol, procaterol* for inhalatory or oral application:
  - effect begins after the inhalation in 10 minutes
  - maximum - in 2-3 h
  - duration of action - 12 h
- Highly lipophilic, entry & retention in bronchial smooth muscle, long-lasting effect

The role of LABA in stable asthma



- LABA monotherapy should not be used in the management of stable asthma

- Addition of LABA to ICS is the preferred choice when symptoms are uncontrolled despite ICS monotherapy in moderate doses

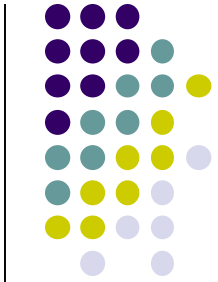
Methylxantines

- **Pharmacodynamics of *methylxantines:***

  - CNS
  - cardiovascular effects
  - GIT
  - kidneys
  - smooth muscle

- *Theophylline, theobromine, caffeine -* alcaloids in tea, cocoa & coffee

Use of methylxantines

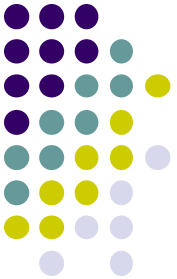


- ***Theophylline***

- *aminophylline* - salt with 86% of *theophylline* base

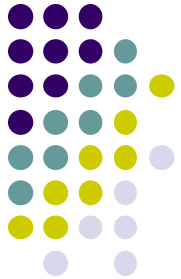
- microcrystalic form with larger surface ⇑ dilution & total absorption after oral application

Methylxantines
SE



- Blood levels should be monitored
- Therapeutic & toxic effects directly correlate with blood levels
- Amelioration of lung effects – 5 - 20 mg/l
- Anorexia, nausea, vomitting, abdominal problems, headache & anxiety > 20 mg/l
- > 40 mg/l cramps & arrhythmias

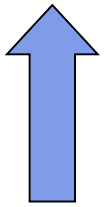
Methylxantines
PK



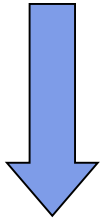
- Plasmatic clearance in adults - 0.69 ml/kg/min - 0,041 l/kg/h
- Changes in hepatal functions (cirrhosis, heart failure, virus hepatitis) ⇓ clearance
- Induction of hepatal enzymes (smoking, long-therm therapy with inducers) ⇑ clearance, need for about 30% ⇑ of dose
- Children = faster clearance of *theophylline* (1 - 1.5 ml/kg/min - 0.06 - 0.09 l/kg/h)

Methylxantines
Interactions

- Biologic halflife of *theophylline:*

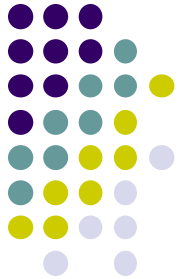


Erythromycin (macrolides), cimetidine, ciprofloxacin, oral contraceptives



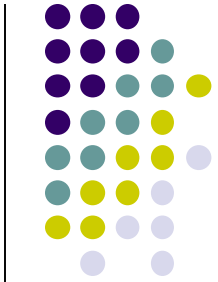
Phenytoin, carbamazepine, rifampicin, phenobarbital

Drug forms with sustained release



- Maintain therapeutic levels of *theophylline* - 12 to 24 h
- Minor level fluctuation
- Less frequent application
- More effective in night bronchospasm prevention

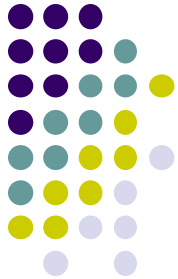
M-receptor antagonists



- ***Ipratropium bromide*** – short-acting bronchodilatant
- In patients with **cardiac diseases or thyreotoxicosis**, where sympathomimetics are contraindicated
- Minimal SE

- ***Tiotropium*** – long-acting bronchodilatant
- Addition of *tiotropium* compared with:
  - doubling inhaled *steroid*
  - addition of *salmeterol*
- Most secondary outcomes favored *tiotropium*

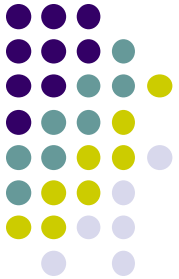
Drugs for the treatment of severe asthma



Anti-IgE therapy (biologic antibody therapy)

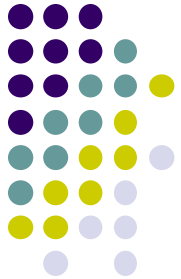
- ***Omalizumab –*** binds IgE in the circulation & prevents it from activating mast cells & basophils
- In moderate & severe asthma it reduces exacerbation rate & steroid dose needed
- It is recommended as an add-on to optimized standard therapy in asthmatics 12 years & older who need continuous or frequent treatment with oral corticosteroids

Anti-IL-13 drugs



- ***Lebrikizumab -*** anti-IL-13 therapy
- MAb that targets IL-13 (a key effector cytokine in Type 2 airway inflammation in asthma) & is currently in advanced stages of development
- It has the potential to block several downstream signals that play a role in disease progression including:
  - airway inflammation
  - mucous hypersecretion
  - airway remodeling
  - the effects are more marked in individuals with high serum **periostin** levels (they reflect underlying IL-13 activity)

Monoclonal anti-lL-5 MAb



Mepolizumab

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

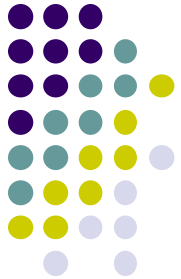
- treatment of **severe asthma** in patients aged 12 years or older & with an eosinophilic phenotype in combination with other antiasthmatics

SE:

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

Medications to Treat Asthma

Summary of Long-Term Control



- Taken daily over a long period of time

- Used to reduce inflammation, relax airway muscles, & improve symptoms & lung function:

  - Inhaled ***corticosteroids***
  - Long-acting ***β_2-agonists***
  - Leukotriene modifiers

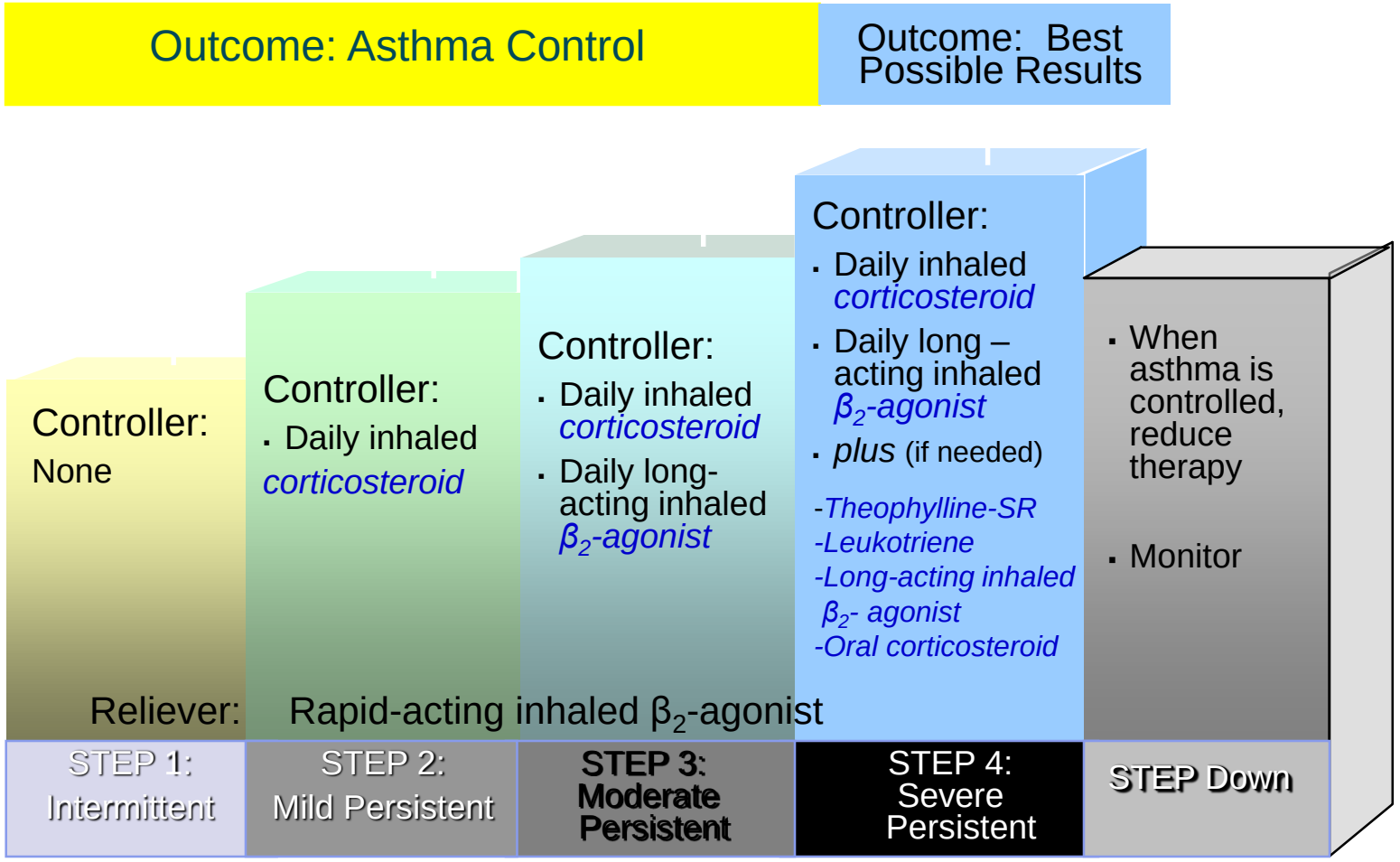
Medications to Treat Asthma

Summary of Quick-Relief

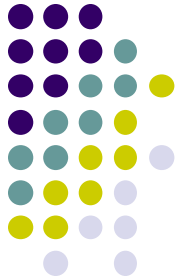
- Used in acute episodes
- Generally short-acting ***β_2-agonists***
- ***Ipratropium, tiotropium***
- Oral & i.v. ***GC***

Stepwise approach to Asthma Therapy

Adults



Basic principles in COPD treatment



- **Each pharmacological treatment regimen needs to be:**
  - patient-specific
  - guided by severity of symptoms
  - guided by risk of exacerbations
  - drug availability
  - patient's response
- **None of the existing medications for COPD has been conclusively shown to modify the long-term decline in lung function**

Drugs used in COPD treatment

- **They copy drug arsenal used in treatment of asthma:**

- bronchodilating drugs *(β_2-mimetics, anticholinergics)*
- methylxantines *(theophylline, aminophylline)*
- inhalatory corticosteroids *(beclomethsone, budesonide, fluticasone)*
- systemic corticosteroids *(prednisone, methylprednisolone)*
- phosphodiesterase-4 inhibitor *(roflumilast)*

- It is possible to combine ***β_2-mimetics*** with an ***anticholinergic*** or ***corticosteroid***

Bronchodilating drugs used in COPD

β_2-agonists			
Short-acting	**h**	**Long-acting**	**h**
fenoterol	4 - 6	*formoterol*	12
salbutamol	4 - 6	*indacaterol*	24
Anticholinergics			
Short-acting	**h**	**Long-acting**	**h**
ipratropium	6 - 8	*aclidinium*	12
oxitropium	7 - 9	*tiotropium*	24

Roflumilast

- Long-acting selective PDE-4 inhibitor
- Anti-inflammatory effects
- **Indicated** in **severe COPD** with **chronic bronchitis**

- **SE:**
  - GI (diarrhea, nausea, abdominal pain, weight loss, loss of appetite)
  - neurologic (headache, insomnia, depression)
  - infections (sinusitis, rhinitis, uro-infections)